UNIVERSITÄT BERN

Graduate School for Health Sciences

University of Bern

Investigation of robotics-assisted tilt table technology for cardiopulmonary exercise testing in stroke patients

PhD Thesis submitted by

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for the degree of

PhD in Health Sciences (Rehabilitation Science)

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Table of contents

Abstract

Due to the lack of exercise testing devices that can be employed in stroke patients with severe disability, the aim of this PhD research was to investigate the clinical feasibility of using a robotics-assisted tilt table (RATT) as a method for cardiopulmonary exercise testing (CPET) and exercise training in stroke patients. For this purpose, the RATT was augmented with force sensors, a visual feedback system and a work rate calculation algorithm. As the RATT had not been used previously for CPET, the first phase of this project focused on a feasibility study in 11 healthy able-bodied subjects. The results demonstrated substantial cardiopulmonary responses, no complications were found, and the method was deemed feasible. The second phase was to analyse validity and test-retest reliability of the primary CPET parameters obtained from the RATT in 18 healthy able-bodied subjects and to compare the outcomes to those obtained from standard exercise testing devices (a cycle ergometer and a treadmill). The results demonstrated that peak oxygen uptake ($V'O_{2peak}$) and oxygen uptake at the submaximal exercise thresholds on the RATT were ~20% lower than for the cycle ergometer and ~30% lower than on the treadmill. A very high correlation was found between the RATT vs the cycle ergometer $V'O_{2peak}$ and the RATT vs the treadmill $V'O_{2peak}$. Test-retest reliability of CPET parameters obtained from the RATT were similarly high to those for standard exercise testing devices. These findings suggested that the RATT is a valid and reliable device for CPET and that it has potential to be used in severely impaired patients. Thus, the third phase was to investigate using the RATT for CPET and exercise training in 8 severely disabled stroke patients. The method was technically implementable, well tolerated by the patients, and substantial cardiopulmonary responses were observed. Additionally, all patients could exercise at the recommended training intensity for 10 min bouts. Finally, an investigation of test-retest reliability and four-week changes in cardiopulmonary fitness was carried out in 17 stroke patients with various degrees of disability. Good to excellent test-retest reliability and repeatability were found for the main CPET variables. There was no significant difference in most CPET parameters over four weeks. In conclusion, based on the demonstrated validity, reliability and repeatability, the RATT was found to be a feasible and appropriate alternative exercise testing and training device for patients who have limitations for use of standard devices.

1. Introduction

1.1 Stroke

Stroke is characterized as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral haemorrhage (ICH), and subarachnoid haemorrhage (SAH) (Sacco et al., 2013). Stroke is a major cause of death and disability (Sacco et al., 2013). Annually, 15 million people suffer a stroke worldwide; one-third die and one-third are permanently disabled (Mackay and Mensah, 2004). In Europe, the incidence of stroke ranges from 101.1 to 239.3 per 100,000 in men and 63.0 to 158.7 per 100,000 in women (Heuschmann et al., 2009). The incidence is projected to increase as a result of a higher proportion of older people in the population in the future (Truelsen et al., 2006).

Most stroke insults are not fatal but affect physical and psychological function (Singh et al., 2000;Lai et al., 2002;Jonsson et al., 2005). The physical impairments are related to the area of brain damage, which can involve motor and sensory impairments, cognitive impairments, communication or swallowing (Brott et al., 1989;Patel et al., 2002). Stroke imposes a substantial impact on the individual, family and society (Scholte op Reimer et al., 1998;Hickenbottom et al., 2002). The burden of stroke is high especially in people aged 80 years or over, which contributes to about one-third of health care utilization (Marini et al., 2004).

1.2 Cardiopulmonary fitness after stroke

Cardiopulmonary fitness is related to the ability to perform large muscle, dynamic, moderate to vigorous intensity exercise for prolonged periods of time (Pescatello et al., 2014). Maximal or peak oxygen uptake ($V'O_{2max}$ or $V'O_{2peak}$), which reflect the integrative cardiopulmonary response to transport oxygen to muscle and the ability of the muscle cells to utilize it, is the most often considered criterion for cardiopulmonary fitness (McArdle et al., 1996;Wasserman et al., 1999;Pescatello et al., 2014). Patients after stroke have severely reduced cardiopulmonary fitness – their peak oxygen uptake ($V'O_{2peak}$) is in the range of 8-22 mL/kg/min which is approximately 26-87% of their age and sex-matched peers (Smith et al., 2012).

Cardiopulmonary fitness predicts the risk for cardiovascular disease, guides the prognosis for functional recovery, and is associated with the degree of independence in stroke patients (Smith et al., 2012;Kim et al., 2014). The low $V'O_{2peak}$ is associated with an increased incidence of cardiovascular disease and recurrent stroke (Smith et al., 2012). Additionally, it was reported that baseline $V'O_{2peak}$ negatively correlated with changes in $V'O_{2peak}$ after aerobic exercise training: individuals with the most compromised fitness level were found to gain the greatest benefit from an exercise intervention (Tang et al., 2013b).

1.3 Cardiopulmonary exercise testing (CPET) in stroke patients

In 2014, the American Heart Association Stroke Council recommended that individuals after stroke undergo cardiopulmonary exercise testing (CPET) as part of a medical evaluation before beginning an exercise programme (Billinger et al., 2014). The results obtained from CPET can be used to assess the patient's aerobic capacity, to prescribe the optimal exercise intensity for training and to follow up after exercise intervention (Marzolini et al., 2012;Billinger et al., 2014). The implementation of CPET in an exercise programme correlates well with the aims of stroke rehabilitation which are to decrease the rates of recurrent stroke and cardiovascular events, to prevent complications of prolonged inactivity and to increase cardiopulmonary fitness (Gordon et al., 2004).

A systematic review examining the safety of CPET in stroke patients found only 11 adverse events from 876 CPETs (1.26%) (van de Port et al., 2015). Cardiovascular adverse events associated with CPET were reported in individual studies to be in the range of 0 to 11% (Kelly et al., 2003;Tang et al., 2006;Chen et al., 2010;Marzolini et al., 2012;Billinger et al., 2014). These included abnormal blood pressure (hypertensive response), ST segment depression, complex ventricular premature beats or ventricular tachycardia (Tang et al., 2006;Marzolini et al., 2012).

1.4 Exercise training in stroke patients

Exercise improves cardiopulmonary fitness, which has a positive effect on functional capacity in patients' daily activities (Macko et al., 2001). Short term exercise was shown to improve cardiopulmonary fitness and walking endurance in patients after stroke (Duncan et al., 2003;Eich et al., 2004;Tang et al., 2009b). Moreover, exercise plays a role as a lifestyle intervention to prevent recurrent stroke and cardiac disease (Goldstein et al., 2006). It was found that the five main strategies, which are dietary modification, exercise, aspirin, a statin, and an antihypertensive agent, reduce the risk of recurrent vascular events by 80% in patients after stroke or transient ischemic attack (Hackam and Spence, 2007).

Exercise after stroke is challenging due to barriers such as patient-related factors (e.g. depression, lack of interest, lack of motivation) and practical factors (lack of transportation, lack of availability of fitness resources) (Billinger et al., 2014). A survey of cardiac rehabilitation in 40 facilities showed that only 60% of the facilities enrolled stroke patients (Tang et al., 2009a). Nearly half of those which enrolled stroke patients accepted only patients as a secondary diagnosis or only with mild to moderate impairments (Tang et al., 2009a). Some programmes accepted only mild and nondisabling cases: the most common reasons for rejecting participants were impaired walking ability (Tang et al., 2009a). The promotion of exercise in stroke survivors with moderate to severe disabilities would be challenging (Billinger et al., 2014). It was proposed that the barriers may be overcome by providing alternative exercise modalities which do not require trunk stability or independent limb control (Tang et al., 2009a).

1.5 Current limitations of standard devices for CPET and exercise training in stroke patients

Most CPET studies in stroke patients employed a cycle ergometer or a treadmill (Smith et al., 2012). Unlike patients with heart or lung problems, stroke patients are a unique population with significant disabilities. Weakness, balance, coordination problems or insecurity i.e. a fear of falling, play an additional role in patients' performance in CPET. It was found that stroke patients usually terminated CPET because of fatigue or problems related to neuromuscular function instead of dyspnea or breathing effort (Tang et al., 2013a), which means that peripheral limitations play a larger role than cardiopulmonary limitations in test termination.

The treadmill is considered the gold standard device for CPET in normal subjects. The peak cardiopulmonary performance values obtained from the treadmill are higher than those obtained from the cycle ergometer (Porszasz et al., 2003). Most people are more familiar with the movement of walking/running than cycling. However, exercise testing on a treadmill requires good walking ability, thus limiting its usability in moderately to severely disabled stroke patients. Additionally, walking ability and cardiopulmonary fitness in stroke are not necessary correlated (Outermans et al., 2015): although the ability to walk is related to cardiopulmonary fitness in abled-bodied subjects, it was found that in stroke patients the ability to walk is also related to balance, weakness or coordination problems (Pohl et al., 2002;Pradon et al., 2013). It was shown that patients' $V'O_{2peak}$ increased by approximately 10% ($V'O_{2peak}$ improved from 20.6 to 22.5 mL/kg/min) with the use of an ankle-foot orthosis to stabilize the ankle during CPET on a treadmill, supporting the observation that patients stopped exercise because of neuromuscular limitations rather than cardiopulmonary limitations (Hyun et al., 2015).

The cycle ergometer is the most common device used for CPET in stroke patients: less coordination is required and the risk of falling is lower than on the treadmill (Maeder et al., 2005). However, studies that recruited stroke patients with mild to moderate disabilities reported that up to 3/4 of the patient exclusions were related to the set-up on the cycle ergometer (adductor spasticity, muscle weakness or reduced joint range of motion, and inability to perform the cyclical motion on the cycle ergometer) (Chu et al., 2004;Yates et al., 2004). A semi-recumbent cycle ergometer provides a back rest and leg support to secure the lower extremities, thus enabling more patients to be tested (Carr and Jones, 2003;Tang et al., 2006;Tomczak et al., 2008;Billinger et al., 2014).

Recent systematic reviews found that there is a lack of data on cardiopulmonary fitness in patients with severe stroke disability which may be because of the limitations of the treadmill and the cycle ergometer for testing in these patients (Stoller et al., 2012;Marsden et al., 2013). It is expected that the overall $V'O_{2peak}$ in stroke patients would have been lower if the studies had tested severely disabled stroke patients (Smith et al., 2012;Marsden et al., 2013). Exercise testing and training in severely disabled patients is understudied.

1.6 Alternative devices for CPET in stroke patients

Several alternative devices have been investigated to address the lack of appropriate testing devices in stroke patients. A total body recumbent stepper is a device generally used in fitness centres. It enables patients with balance or coordination problems to be tested and promotes both upper and lower extremity exercise (Billinger et al., 2008b). It is a validated device for CPET in both normal subjects and chronic stroke patients (Billinger et al., 2008a;Billinger et al., 2008b). The $V'O_{2peak}$ achieved on the total body recumbent stepper is higher than the cycle ergometer, which may be due to the higher muscle mass used and lower fatigue during exercise (Billinger et al., 2008b).

Robotics-assisted treadmill exercise was investigated for exercise testing and training. Although there is no validation study in normal subjects, it has been used in patients after spinal cord injury and stroke (Jack et al., 2010;Stoller et al., 2014a). Using this type of device for exercise provides advantages of repetitive task-orientated training for walking together with cardiopulmonary exercise at the same time (Stoller et al., 2015). However, there are some limitations of this device. Firstly, the difficulty and time needed for patients to be attached to the robotic orthoses. Secondly, during exercise the patients need to apply forces and there is a high coordinative demand to control the walking direction while the exoskeleton restricts the movement. Therefore, patients terminated the tests because of muscular or coordinative fatigue rather than cardiopulmonary limitations (Stoller et al., 2014a). Finally, studies reported that 28.6 to 45.5% of stroke patients training on the robotics-assisted treadmill experienced skin-related problems when active participation was required (skin problems/pain from pressure or rubbing of straps or cuffs), although careful fitting of the straps and the addition of extra padding were provided (Kelly et al., 2013;Stoller et al., 2015). This problem was usually found in weaker patients who had difficulty maintaining knee extension during the stance phase (Kelly et al., 2013).

Another potential device is an end-effector-based stair climbing and walking robot. However, to date, only a feasibility study of CPET using this device in healthy able-bodied subjects was done and it has not yet been tested for CPET in patient populations (Stoller et al., 2014b).

1.7 Novel device for CPET and exercise training in stroke patients: a robotics-assisted tilt table

A robotics-assisted tilt table (RATT) is a motorized tilt table with a body harness to support the body and two motor drives to provide cyclical movement of the legs (e.g. Erigo, Hocoma AG, Switzerland). Two thigh cuffs fix the legs and interface to the leg drives, and two foot plates support the feet. It is used clinically in severely disabled neurological patients for early mobilization and intensive sensorimotor stimulation. This is done by the RATT tilting the patient upright, and moving and providing cyclical loading for the patient's lower limbs. During the therapy, the RATT can be tilted up from 0 to 80 degrees and the cyclic leg movement can be set to a stepping cadence between 8 and 80 steps/min.

The RATT has potential for the implementation in CPET and exercise training in patients with disability. The reasons are as follows:

1. The body harness provides adequate security for patients with balance or coordination problems or fear of falling. The total body support lessens the chance of exercised-related injuries.
2. The thigh cuffs and foot plates secure the lower extremities, which enables patients with severe lower extremity weakness or spasticity to exercise. Additionally, the foot plate can be adjusted to deformity such as ankle equinus from gastrocnemius-soleus spasticity.
3. It takes 5 to 10 minutes to fit the patient on the RATT. The patients can be transferred to the RATT both in lying and sitting positions.
4. In case of emergency, the RATT can be tilted down and all the straps can be released immediately. Emergency medical care, if required, can be done on the RATT.

The RATT was augmented with force sensors and a visual feedback system so that severely disabled neurological patients can actively participate in exercise testing and training on the device (Bichsel et al., 2011). The visual feedback screen gives direct performance feedback during exercise and is a motivating factor.

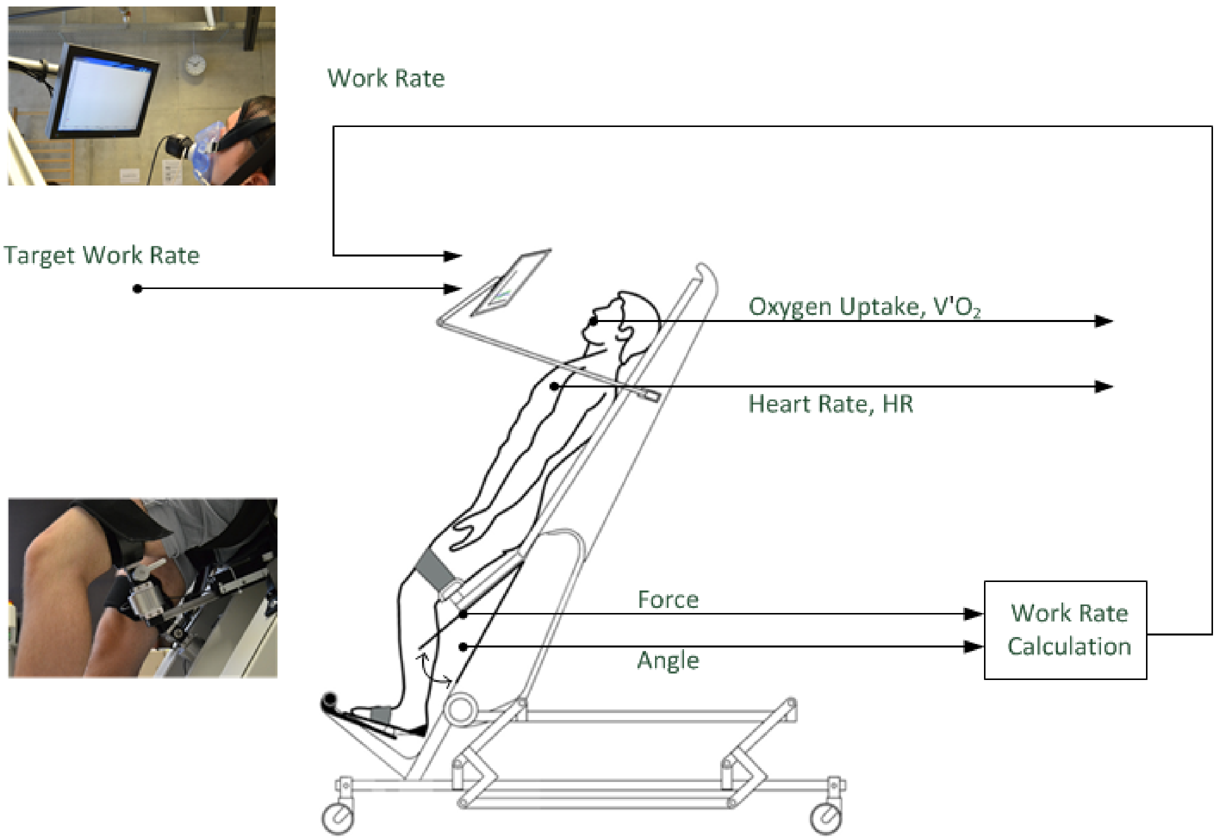

Figure 1. Robotics-assisted tilt table (RATT) with visual feedback system. The visual feedback screen shows the target work rate and the subject's work rate. The subject's work rate was calculated from the forces in the thigh cuffs and the angular velocities.

We proposed that this device may be appropriate for cardiopulmonary exercise testing and training in patients who have severe neurological deficits, including severely-disabled stroke patients. However, there is a lack of basic knowledge and supportive evidence for the use of the RATT. This PhD project was carried out to address these open questions.

2. Empirical Contribution

Due to the lack of exercise testing devices that can be employed in stroke patients with moderate to severe disability, the aim of the PhD project was to investigate the clinical feasibility of using the augmented RATT as a method for cardiopulmonary exercise testing and training in stroke patients.

As the RATT had not been used previously for exercise testing and training, the study was planned using a stepwise approach beginning with a feasibility study in healthy able-bodied subjects. Then, comparative and test-retest reliability analyses for cardiopulmonary performance parameters obtained from the RATT and standard exercise devices (cycle and treadmill ergometers) were done. Following these investigations of feasibility, validity and reliability of this new method in healthy able-bodied subjects, a feasibility study of exercise testing and training in severely disabled stroke patients was done. Finally, an investigation of test-retest reliability and longitudinal changes in cardiopulmonary fitness was done in stroke patients with various degrees of disability.

Thus, we defined 4 main objectives:

1. To conduct a feasibility study using the RATT for cardiopulmonary exercise testing in healthy able-bodied subjects.
2. To compare cardiopulmonary performance parameters and test-retest reliability achieved from the RATT, a cycle ergometer and a treadmill in healthy able-bodied subjects.
3. To evaluate the clinical feasibility of the RATT for cardiopulmonary exercise testing and training in severely disabled, non-ambulatory stroke patients.
4. To analyse test-retest reliability and to prospectively study changes in cardiopulmonary fitness over 4 weeks in stroke patients with various degrees of disability using the RATT.

The original publications corresponding to each of these objectives, are presented in Chapter 3:

- Objective 1: the feasibility study using the RATT for cardiopulmonary exercise testing was done in 11 healthy able-bodied subjects (Chapter 3.1).
- Objective 2: Chapter 3.2 presents a comparison of peak cardiopulmonary exercise performance parameters obtained from the RATT, a cycle ergometer and a treadmill using 18 healthy able-bodied subjects. Test-retest reliability of the peak cardiopulmonary performance parameters was also quantified. Further analysis to compare submaximal exercise parameters from the RATT, a cycle ergometer and a treadmill is reported in Chapter 3.3.
- Objective 3: Chapter 3.4 presents the results of the feasibility study of cardiopulmonary exercise testing and training in 8 dependent-ambulatory stroke patients.
- Objective 4: chapter 3.5 presents the result of test-retest reliability analysis and the prospective 4-week changes in cardiopulmonary fitness in 17 stroke patients.

A general discussion and an overall outlook are presented in Chapter 4.

3. Methods and Results (Original Publications)

3.1 Cardiopulmonary performance testing using a robotics-assisted tilt table: feasibility assessment in able-bodied subjects

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Published as:

Saengsuwan, J., Laubacher, M., Nef, T., and Hunt, K.J. (2014). Cardiopulmonary performance testing using a robotics-assisted tilt table: feasibility assessment in able-bodied subjects. Technology and Health Care. 22(2):179-187.

Abstract

Background: Robotics-assisted tilt table technology was introduced for early rehabilitation of neurological patients. It provides cyclical stepping movement and physiological loading of the legs. The aim of the present study was to assess the feasibility of this type of device for peak cardiopulmonary performance testing using able-bodied subjects.

Methods: A robotics-assisted tilt table was augmented with force sensors in the thigh cuffs and a work rate estimation algorithm. A custom visual feedback system was employed to guide the subjects' work rate and to provide real time feedback of actual work rate. Feasibility assessment focused on: (i) implementation (technical feasibility), and (ii) responsiveness (was there a measurable, high-level cardiopulmonary reaction?). For responsiveness testing, each subject carried out an incremental exercise test to the limit of functional capacity with a work rate increment of 5W/min in female subjects and 8 W/min in males.

Results: 11 able-bodied subjects were included (9 male, 2 female; age 29.6 ± 7.1 years: mean ± SD). Resting oxygen uptake ($\dot{V}O_2$) was 4.6 ± 0.7 mL/min/kg and $\dot{V}O_2$peak was 32.4 ± 5.1 mL/min/kg; this mean $\dot{V}O_2$peak was 81.1% of the predicted peak value for cycle ergometry. Peak heart rate (HRpeak) was 177.5 ± 9.7 beats/min; all subjects reached at least 85% of their predicted HRpeak value. Respiratory exchange ratio (RER) at $\dot{V}O_2$peak was 1.02 ± 0.07. Peak work rate was 61.3 ± 15.1 W. All subjects reported a Borg CR10 value for exertion and leg fatigue of 7 or more.

Conclusions: The robotics-assisted tilt table is deemed feasible for peak cardiopulmonary performance testing: the approach was found to be technically implementable and substantial cardiopulmonary responses were observed. Further testing in neurologically-impaired subjects is warranted.

1. Introduction

Maximal oxygen uptake ($\dot{V}O_2max$) or peak oxygen uptake ($\dot{V}O_2peak$) is often used in evaluation of physical fitness (Buchfuhrer et al., 1983;Basset and Boulay, 2000). This value is of obvious clinical importance as it provides objective information on the functional status of the cardiovascular, pulmonary and musculoskeletal systems (Bassett and Howley, 2000;Sagiv et al., 2007). It can also be used to guide exercise prescription and to predict cardiovascular survival (Koelling et al., 2004;O'Neill et al., 2005;Kodama et al., 2009).

The most widely recommended and used devices for measuring maximal cardiopulmonary performance are the treadmill and the cycle ergometer (Myers et al., 1991;Maffeis et al., 1994;Bader et al., 1999). However, both the treadmill and the cycle ergometer may have limitations when used in patients with neurological problems. Thus there is limited information about $\dot{V}O_2peak$ in stroke patients and often the protocols have to be modified or additional support is needed (Macko et al., 1997;Yates et al., 2004;Tang et al., 2006). Even with modifications or external support for the treadmill or cycle ergometer, severely compromised patients often have problems in performing the test.

Robotics-assisted tilt table (RATT) technology with integrated leg drives for basic stepping functionality is clinically available for patients with neurological impairments. Initially introduced for early rehabilitation, it provides cyclical stepping movement and physiological loading in immobilized patients or patients on long bed rest. This technology provides stability and support in patients with neurological disorders such as stroke for whom weakness, balance and coordination problems would preclude cardiopulmonary performance testing using a conventional device. In our research to date, the functionality of this device has been extended by adding force sensors, work rate calculation and a visual feedback system to guide exercise intensity during cardiopulmonary testing and training (Bichsel et al., 2011).

We propose that this device may facilitate the estimation of $\dot{V}O_2peak$ and other important cardiopulmonary performance parameters in patients who have neurological deficits. However, there is currently a lack of feasibility data to assess implementability and responsiveness of the augmented RATT device for cardiopulmonary performance testing even in the healthy population. Therefore, the aim of the present study was to assess the feasibility, i.e. implementation and responsiveness, of the augmented RATT device for peak cardiopulmonary performance testing using able-bodied subjects.

2. Methods

Ethics statement

The study was reviewed and approved by the ethics committee of the Swiss Canton of Bern (Kantonale Ethikkommission (KEK) Bern). Written informed consent was obtained from all subjects prior to participation.

Subjects

Eleven subjects were recruited (Table 1) and all completed the tests. All subjects reported no neuromuscular, pulmonary, cardiovascular or musculoskeletal impairments that might have precluded maximal performance testing.

Table 1. Subject data. Predicted HRpeak is 220 – age. Predicted $\dot{V}O_2peak$ calculated according to Wasserman et al. (1999).

Characteristic	**Value** – mean (SD)
Age [years]	29.6 (7.1)
Male/Female [n]	9/2
Height [cm]	173.6 (10.0)
Body mass [kg]	69.2 (13.4)
Body mass index [kg/m^2]	22.8 (2.4)
Predicted HRpeak [beats/min]	190 (7)
Predicted $\dot{V}O_2peak$ [L/min]	2.8 (0.6)

Robotics-assisted tilt table

A robotics-assisted tilt table was employed (Erigo, Hocoma AG, Switzerland) which was augmented with force sensors in the thigh cuffs together with a work rate estimation algorithm (Figure 1). A custom visual feedback system was used to guide the subjects' work rate and to provide real time feedback of actual work rate (Figure 2). The step frequency was set as 80 steps/min and range of motion of the hip joints as 10-35 degrees.

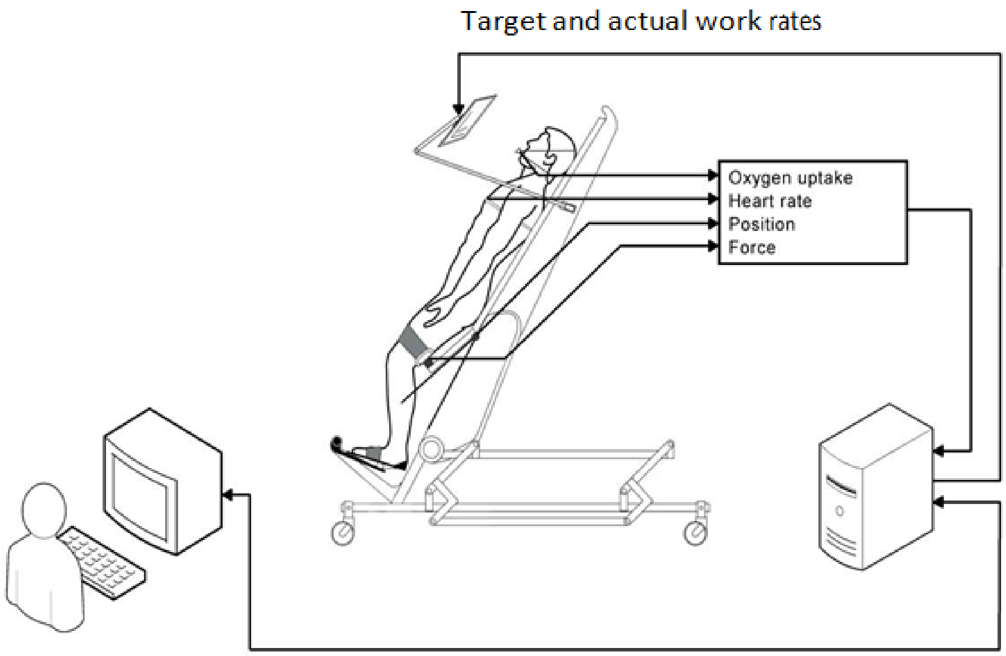

Figure 1. Work rate estimation and visual feedback. The subject's work rate is estimated continuously from forces in the thigh cuffs and joint angular velocities. A target work rate profile is displayed with the estimated work rate and the subject must adapt volitional muscular work to maintain the target. Physiological variables are monitored continuously

Figure 2. The augmented robotics-assisted tilt table (RATT) system with force sensors under the thigh cuffs, visual feedback system and breath-by-breath cardiopulmonary monitoring system.

Procedures

Subjects were instructed to avoid strenuous activity within the 24 hours before testing and not to consume nicotine, caffeine or a large amount of food at least 3 hours prior to testing.

Each subject performed 1 incremental exercise test on the augmented RATT. Prior to the incremental phase of the test, the protocol included a warm up and passive measurement (Figure 3). The subjects initially lay horizontal on the tilt table and were secured in accordance with the provisions of the support system. The thighs and the feet were fixed to the thigh cuffs and foot straps respectively. The test protocol was explained to the subject and the measurement and gas exchange monitoring systems were introduced. The subject was then tilted up to 70 degrees and the formal test protocol (Figure 3) commenced: there was a recorded rest phase of 3 minutes followed by a warm up phase of exercising at a work rate of 15 W for 5 minutes. Then subjects had 3 minutes of rest for recovery and 3 minutes for "passive," unloaded movement before the incremental exercise phase. During unloaded movement the device was active while the subject was instructed to remain passive. For the incremental exercise phase, the work rate increment was 5 W/min in females and 8 W/min in males. This phase was terminated volitionally by the subjects after they could no longer maintain the work rate target and had reached their functional limit. After the incremental exercise phase there was a passive phase for 3 minutes for recovery. To maintain the target work rate, the subject was instructed to actively push upwards and downwards into the thigh cuffs in the direction of motion.

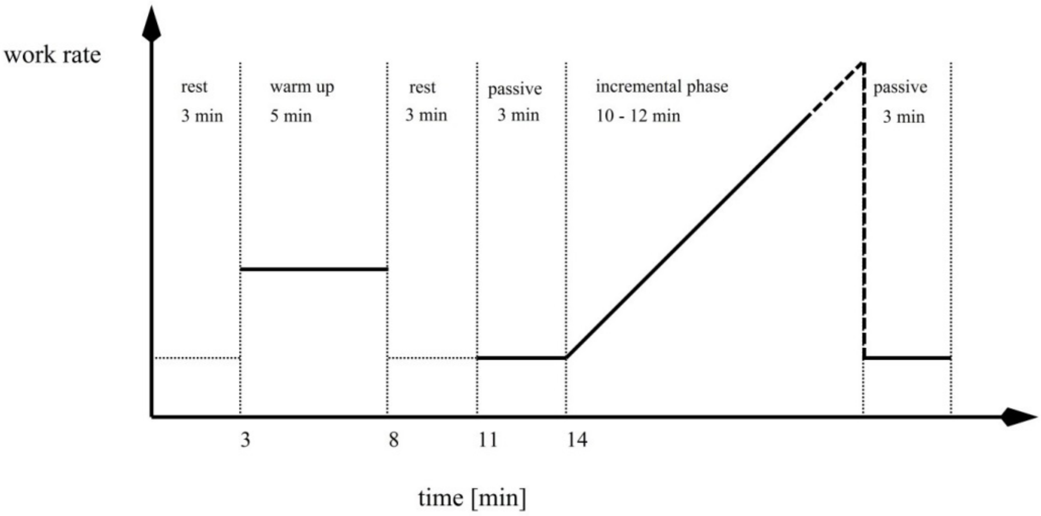

Figure 3. Exercise testing protocol. The line indicates the target work rate profile that the participant was instructed to follow by actively producing forces.

Measurements

Cardiopulmonary response variables were monitored in real time using a breath-by-breath system (MetaMax 3B, Cortex Biophysik GmbH, Germany). Pressure, volume and gas calibration was performed each day prior to testing according to the manufacturer's recommendations: volume was calibrated using a volumetric syringe and gas was calibrated using a certified precision gas mixture. Heart rate (HR) was continuously measured and recorded by a chest belt (T31, Polar Electro, Kempele, Finland) and a receiver board (HRMI, Sparkfun, Boulder, USA). Subjects rated perceived exertion every 3 minutes during the incremental phase using the Borg CR10 scale for dyspnea and leg fatigue.

Outcome measures and data analysis

The cardiopulmonary performance parameters were calculated as follows: $\dot{V}O_2peak$ was obtained from a 30-second moving average of $\dot{V}O_2$; respiratory exchange ratio (RER) at $\dot{V}O_2peak$ was also obtained from a 30-second moving average value of RER; peak heart rate (HRpeak) was the highest heart rate value reached during the incremental exercise test protocol; peak work rate (WRpeak) was calculated from a 10-second moving average of the estimated work rate; the Borg CR10 scale for both exertion and leg fatigue was recorded at the time the subject reached their maximal performance; the slope of the $\dot{V}O_2$–WR relationship was calculated using data from 1 minute after the start of the ramp phase until 1 minute before termination of the ramp phase. The time to $\dot{V}O_2peak$ and the subjective reason for test termination were also recorded. The predicted HRpeak was calculated as 220 – age and the predicted $\dot{V}O_2peak$ for cycle ergometry was calculated based on the Wasserman et al. (1999) prediction. All analyses were performed using SPSS version 19 (IBM Corporation, USA).

3. Results

(i) Implementation. When subjects perform volitional muscle activation and increase their work rate, the electric motors in the RATT system operate in braking (generating) mode in order to resist the subject's force and maintain the pre-programmed joint trajectories. During initial tests, it was found that at high levels of work rate towards the end of the incremental phase the device's power supply was not able to buffer the excess energy produced, resulting in failure of the motors' servo-control electronics. To solve this problem, in order to buffer the excess energy produced during high levels of volitional muscular effort, the device's power supply unit was augmented with four shunt resistors connected in parallel (model DSR 50/5, Maxon Motor AG, Switzerland). Following this modification no further problems were encountered.

(ii) Responsiveness. All subjects showed substantial cardiopulmonary responses during the ramp phase of the protocol (Figure 4 – typical responses from one subject).

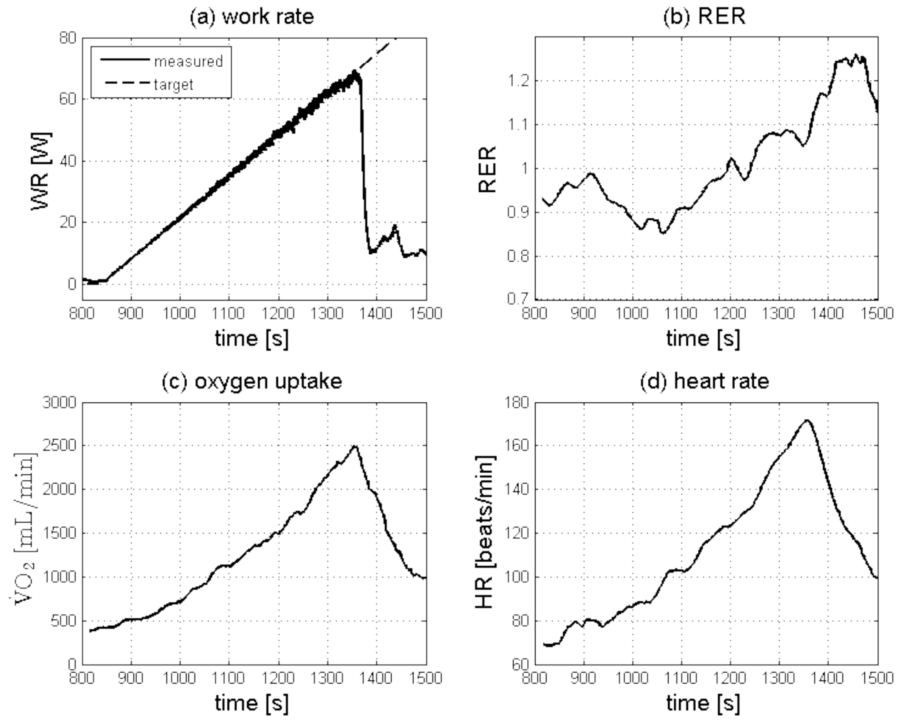

Figure 4. Typical peak cardiopulmonary responses from one subject during the ramp phase of the test protocol. (a) Target and measured work rates, (b) respiratory exchange ratio (RER), (c) oxygen uptake ($\dot{V}O_2$), (d) heart rate (HR). The plots of RER, $\dot{V}O_2$ and HR show averages over a 30s moving window.

The outcome variables used for the responsiveness evaluation, averaged across all subjects, are summarised in Table 2. Resting $\dot{V}O_2$ was 4.6 ± 0.7 mL/min/kg and $\dot{V}O_2$peak was 32.4 ± 5.1 mL/min/kg; this mean $\dot{V}O_2$peak was 81.1% of the predicted $\dot{V}O_2$peak for cycle ergometry (Wasserman et al., 1999). Resting HR was 80.3 ± 10.6 beats/min and HRpeak was 177.5 ± 9.7 beats/min; all subjects reached at least 85% of their predicted HRpeak value. RER at $\dot{V}O_2$peak was 1.02 ± 0.07.

WRpeak was 61.3 ± 15.1 W. The average maximal work rate achieved in males was 65.7 W (n = 9) whereas in females it was 41.5 W (n = 2). The $\dot{V}O_2$-WR relationship had a slope of 31.0 ± 4.5 mL/min/W.

All subjects rated the Borg CR10 scale of exertion and leg fatigue as more than 7, whereby the average value for leg fatigue was higher than that for exertion. The average duration of the incremental exercise phase was 8 min 48 s. Seven subjects achieved their maximal performance within the duration of 8-12 minutes. The reason given for termination was generalized fatigue in four subjects and leg fatigue in four subjects. Two subjects terminated the exercise because of breathing effort and one with foot pain.

Table 2. Summary of outcome variables for responsiveness testing.

Outcome Variable	**Value** – mean (SD)
Initial Rest Phase	
$\dot{V}O_2$ absolute [L/min]	0.31 (0.05)
$\dot{V}O_2$ relative [mL/min/kg]	4.6 (0.7)
HR [beats/min]	80.3 (10.6)
Passive Phase	
$\dot{V}O_2$ absolute [L/min]	0.4 (0.1)
$\dot{V}O_2$ relative [mL/min/kg]	6.1 (1.0)
HR [beats/min]	83.7 (13.5)
Warm Up Phase	
$\dot{V}O_2$ absolute [L/min]	0.8 (0.1)
$\dot{V}O_2$ relative [mL/min/kg]	11.9 (2.4)
HR [beats/min]	95.2 (10.7)
Incremental Phase	
Peak $\dot{V}O_2$ absolute [L/min]	2.2 (0.5)
Peak $\dot{V}O_2$ relative [mL/min/kg]	32.4 (5.1)
Peak heart rate [beats/min]	177.5 (9.7)
RER at peak $\dot{V}O_2$	1.02 (0.07)
Borg CR10 scale exertion	8.1 (1.1)
Borg CR10 scale leg effort	8.8 (0.9)
Peak WR [W]	61.3 (15.1)
Time to peak $\dot{V}O_2$ [min, s]	8, 48 (1, 42)
$\dot{V}O_2$ - WR relationship (slope) [mL/min/W]	30.95 (4.5)

4. Discussion

The aim of the study was to assess the feasibility of the augmented RATT for peak cardiopulmonary performance testing using able-bodied subjects. Feasibility assessment focused on: (i) implementation (technical feasibility), and (ii) responsiveness (was there a measurable, high-level cardiopulmonary reaction?).

(i) Implementation. The results show that it is technically feasible to employ the RATT system augmented with work rate estimation and a visual feedback system for peak cardiopulmonary performance testing. The addition of energy-buffering shunt resistors was required to cope with high levels of work rate occurring towards the end of the ramp phase, but only in the strongest members of the able-bodied subject group studied here. We judge it to be unlikely that this modification will be required when the device is employed in patients following neurological impairment because the patients are generally older and have additional motor weakness.

(ii) Responsiveness. All subjects could understand the task and accurately follow the work rate target by means of the visual feedback system. For more than 70% of subjects, the duration of the incremental phase was in the range 8-12 minutes, which is the recommended time frame for incremental exercise testing (Buchfuhrer et al., 1983). No subject had an incremental-phase duration longer than 12 minutes, whereas the shortest duration was 6 min 30 s in one male subject. It remains important in future work to select the slope of the work rate increment to try and achieve the optimum duration of 8-12 minutes.

All subjects reached at least 85% of their predicted HRpeak, which implies adequate effort for an incremental exercise test (Balady et al., 2010;Guazzi et al., 2012).

The average $\dot{V}O_2peak$ of 32.4 mL/min/kg was 81.1% of the mean predicted peak value for cycle ergometry based on the Wasserman et al. (1999) prediction. However, this was not unexpected as the RATT provides support of most of the subject's body weight and the pattern of movement in the RATT may not provoke such a high level of muscle activity compared to cycle ergometry. Although the $\dot{V}O_2$peak was approximately 20% lower than in cycle ergometry, it still provoked a substantial oxygen uptake response and is higher than the $\dot{V}O_2$peak obtained from arm ergometry since the $\dot{V}O_2$peak obtained from arm ergometry was 30% lower (Astrand and Saltin, 1961).

The recommended criteria for confirmation of a maximal $\dot{V}O_2$ response include a value for RER at peak of RER ≥ 1.10 (Stickland et al., 2012). Nine subjects in the present study did not fulfil this criterion and the average RER at peak was 1.02. Several factors may contribute to the low RER. Firstly, maximum performance may not have been reached as most subjects were unfamiliar with maximal exercise testing. Second, the tests may often have been terminated prematurely due to leg discomfort or fatigue. Third, the increment in work rate, therefore the incremental phase duration, may not have been optimal for each participant (Smith et al., 2006).

The slope of the $\dot{V}O_2$-WR relationship, i.e. the oxygen cost of the work, in the augmented RATT was 31 mL/min/W, which is higher than values reported for treadmill or cycle ergometers (Porszasz et al., 2003). However, compared to robotics-assisted treadmill exercise (Lokomat, Hocoma AG, Switzerland), the $\dot{V}O_2$-WR slope from the RATT was lower (an average of 31 mL/min/W in the RATT compared to 41 mL/min/W in the robotics-assisted treadmill (Jack et al., 2010). The high $\dot{V}O_2$-WR slope in the robotics-assisted treadmill was attributed to a substantial amount of unaccounted work performed during the test (Jack et al., 2010).

It was found that the $\dot{V}O_2$ during passive movement was only 1.3 times higher than resting $\dot{V}O_2$: passive movement in the RATT is clearly insufficient to provoke meaningful cardiopulmonary responses. This finding correlates with a previous study of passive walking during robotics-assisted treadmill exercise which demonstrated that passive walking increased oxygen uptake by a factor of only 1.4 relative to resting $\dot{V}O_2$ (Jack et al., 2011). The HR did not differ substantially between rest (80.3 beats/min) and passive movement (83.7 beats/min). Although the augmented RATT provides cyclical movement and pressure loading in an upright position, our findings show that passive movement does not provide adequate cardiovascular loading at a level sufficient to improve cardiopulmonary fitness. It is clearly necessary to encourage patients to contribute volitional effort during training on the RATT to promote some cardiopulmonary reconditioning simultaneously with the neurorehabilitation, either via a visual feedback system or by verbal cueing.

A major advantage of using the robotics-assisted tilt table for incremental exercise testing is the safe posture and whole-body support. Currently, the lack of appropriate support in other devices (e.g. cycle ergometer or treadmill) is one of the main factors that preclude exercise testing in severely affected neurological patients. The incorporation of force sensors, work rate calculation and a real time visual feedback system in the robotics-assisted tilt table helps to guide each individual's exercise performance. The visual feedback is beneficial in the improvement of performance as patients receive direct and immediate feedback regarding their performance.

There are some limitations associated with the robotics-assisted tilt table. The maximum cadence is 80 steps/min, which can be perceived as too slow at high work rates. The body support provided and the limited range of movement available leads to a lower level of muscle recruitment compared to treadmill exercise, thus contributing to the lower value of $\dot{V}O_2$peak observed. The stepping movement on the RATT differs from normal walking or cycling. However, the movement pattern is not complex and all subjects were able to adopt the movement pattern easily.

Future work will focus on evaluating the test-retest reliability of performance testing with the augmented RATT. A direct comparison of peak cardiorespiratory performance values obtained from the RATT, a treadmill and a cycle ergometer in a single subject group will be conducted. The approach will then be tested in subjects with neurological impairments.

5. Conclusion

The robotics-assisted tilt table augmented with work rate estimation and a visual feedback system is deemed feasible for peak cardiopulmonary performance testing: the approach was found to be technically implementable and substantial cardiopulmonary responses were observed. Based on this evidence using able-bodied subjects, the work-rate-guided robotics-assisted tilt table approach is recommended for further testing within target groups of neurologically-impaired subjects.

3.2 Comparison of peak cardiopulmonary performance parameters on a robotics-assisted tilt table, a cycle and a treadmill

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Published as:

Saengsuwan, J., Nef, T., Laubacher, M., and Hunt, K.J. (2015).Comparison of peak cardiopulmonary performance parameters on a robotics-assisted tilt table, a cycle and a treadmill. *PloS One* 10(4)**:**e0122767.

Abstract

The aim of the study was to compare the magnitude of peak cardiopulmonary performance parameters including peak oxygen uptake (VO_{2peak}) and peak heart rate (HR_{peak}) obtained from a robotics-assisted tilt table (RATT), a cycle ergometer and a treadmill. The strength of correlations between the three devices, test-retest reliability and repeatability were also assessed. Eighteen healthy subjects performed six maximal exercise tests, with two tests on each of the three exercise modalities. Data from the second tests were used for the comparative and correlation analyses. For nine subjects, test-retest reliability and repeatability of VO_{2peak} and HR_{peak} were assessed. Absolute VO_{2peak} from the RATT, the cycle ergometer and the treadmill was (mean (SD)) 2.2 (0.56), 2.8 (0.80) and 3.2 (0.87) L/min, respectively ($p < 0.001$). HR_{peak} from the RATT, the cycle ergometer and the treadmill was 168 (9.5), 179 (7.9) and 184 (6.9) beats/min, respectively ($p < 0.001$). VO_{2peak} and HR_{peak} from the RATT vs the cycle ergometer and the RATT vs the treadmill showed strong correlations. Test-retest reliability and repeatability were high for VO_{2peak} and HR_{peak} for all devices. The results demonstrate that the RATT has potential to be used for exercise testing where limitations exist for use of standard modalities.

1. Introduction

Maximal oxygen uptake (VO_{2max}) or peak oxygen uptake (VO_{2peak}) are commonly used for the evaluation of physical fitness and for exercise prescription (Myers and Nieman, 2010;Marzolini et al., 2012;Pescatello et al., 2014). The most commonly used devices are treadmills and cycle ergometers. The VO_{2max} achieved from cycle ergometry has been observed to be 6-23% lower than from a treadmill (Buchfuhrer et al., 1983;Carter et al., 2000;Porszasz et al., 2003).

There are some limitations to the use of standard devices in neurological patients who have weakness or coordination problem caused by stroke, multiple sclerosis or spinal cord injury (Myers and Nieman, 2010). The alternative recommended devices for these patients are a semi-recumbent cycle ergometer or a total body stepper (Myers and Nieman, 2010), but severely affected patients have limitations that preclude them from using even these devices.

Recent systematic reviews have highlighted the importance of maintaining cardiorespiratory fitness after stroke (Smith et al., 2012) and spinal cord injury (Jacobs and Nash, 2004), but also emphasise the technical difficulty of implementing testing protocols and training programmes in these populations. Smith et al. (2012) included 42 studies in their systematic review of cardiorespiratory fitness after stroke and reported that VO_{2peak} was as low as 26% of that of healthy age- and gender-matched individuals; but, importantly, they noted that "most studies recruited patients with mild stroke" and pointed out that cardiorespiratory fitness is likely substantially lower in more severely affected patients. The reason for inclusion of only mildly-affected patients in the reviewed studies is clear: most studies estimated VO_{2peak} using either a cycle ergometer or a treadmill, exercise modalities which are only usable in the case of mild to moderate impairment.

Robotics-assisted tilt table provides the advantage of body support, cyclical stepping and physiological loading for early rehabilitation. This type of device has been augmented by adding force sensors, work rate calculation and a visual feedback system to guide exercise intensity for exercise testing (Bichsel et al., 2011). In a previous study, it was shown that it is feasible to measure peak cardiopulmonary performance parameters using the augmented

RATT (Saengsuwan et al., 2014;Laubacher et al., 2015). To verify that the device can be used to measure peak cardiopulmonary performance parameters, the RATT should be first be compared with the standard testing devices using able-bodied subjects.

The aim of this study was to compare the magnitude of peak cardiopulmonary performance parameters including peak oxygen uptake (VO_{2peak}) and peak heart rate (HR_{peak}) obtained from the RATT, a treadmill and a cycle ergometer. The strength of correlations between the devices, test-retest reliability and repeatability were also assessed.

2. Materials and methods

Subjects and general study design

The study was reviewed and approved by the Ethics Review Board of the Canton of Bern in Switzerland (Reference No. 002/12). Written informed consent was obtained from all subjects prior to participation. The study was conducted in Bern University of Applied Sciences from December 2012 to September 2013.

Eighteen subjects (10 male, 8 female) completed the study by performing 6 maximal exercise tests, with 2 tests on each of the three exercise modalities. Data from the second tests were used for the comparative and correlation analyses. For 9 subjects, test-retest reliability and repeatability analyses were carried out. The subjects had the following characteristics (mean (SD)): age 28.6 (6.3) years, height 172.4 (9.9) cm, body mass 69.1 (12.8) kg and body mass index 22.7 (2.2) kg/m^2.

Subjects performed a total of 6 tests using a treadmill (Venus, h/p/cosmos GmbH, Germany – 2 tests), a cycle ergometer (LC7, Monark Exercise AB, Sweden – 2 tests) and a RATT (Erigo, Hocoma AG, Switzerland – 2 tests). The test sessions were separated by at least 48 hours but not more than 7 days. The time of day for testing was the same for each subject. Participants were instructed to avoid strenuous activity within the 24 hours before testing and not to consume food, nicotine or caffeine at least three hours prior to testing (Myers et al., 1991;Pina et al., 1995). The individualized, predicted maximum work rates for the treadmill and the cycle ergometer were calculated based on estimation of VO_{2max} (Jurca et al., 2005).

The rate of increase in work rate was then calculated to achieve the predicted peak work rate in 10 minutes.

Experimental procedures

Each incremental exercise test had the same structure. There was 3 minutes of rest, 5 minutes of warm up, a further 3 minutes of rest, and 3 minutes of unloaded movement. The ramp phase followed. Subjects then exercised until they reached their maximal performance and could not maintain the target work rate. Subjects were verbally encouraged to exercise to their limit of functional capacity.

RATT: The subjects were first placed in a horizontal position on the tilt table and secured in accordance with the provisions of the support system. The thighs and the feet were fixed to the thigh cuffs and foot straps. The tilt table then was tilted to 70 degrees and the stepping movement was set at 80 steps/minute. Unloaded movement was achieved by subjects remaining passive while the RATT moved their legs. During the ramp phase, subjects were instructed to actively produce force by pushing into the leg cuffs. The target work rate and measured work rate were visually fed back to the subjects in real time on a computer screen (Figure 1).

Cycle ergometer: The ramp phase was implemented by linearly increasing the work rate on the electromechanical brake. Unloaded movement was achieved by subjects cycling at 0 W. The cycle cadence throughout the test was freely selected but always above 60 rpm. The settings for the seat height, handlebar height and the seat to handlebar distance were adjusted to accommodate each subject. Each individual set up was recorded to ensure the same position in subsequent tests.

Treadmill: Unloaded work was implemented using a low treadmill speed (0.9 km/h) and zero slope. During the ramp phase work rate was increased linearly every 30 seconds using combined non-linear changes in speed and slope (Hunt, 2008).

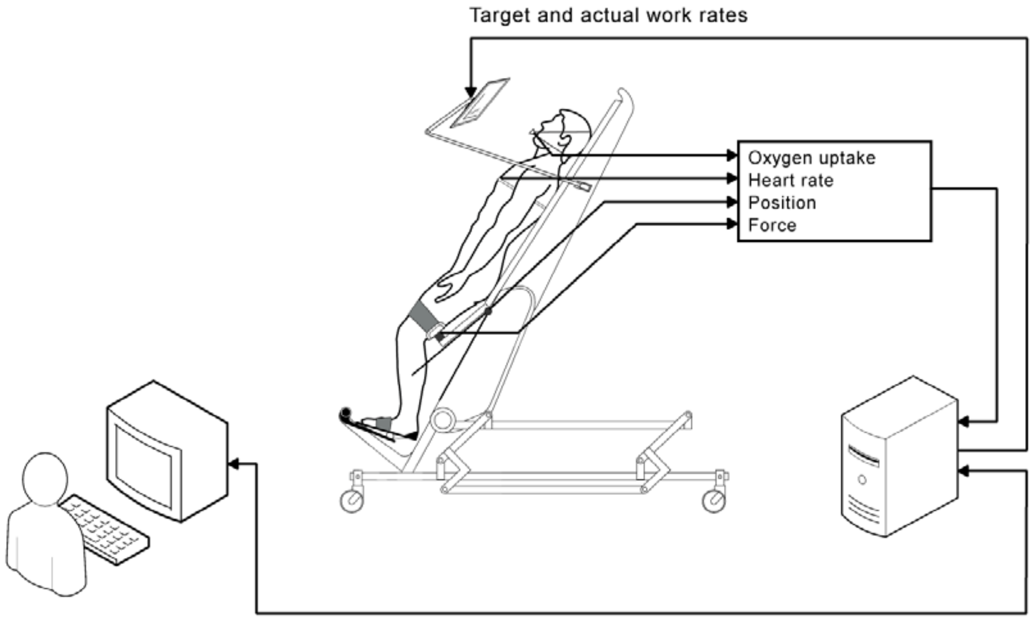

Figure 1. Work rate estimation and visual feedback. The subject's work rate is estimated continuously from forces in the thigh cuffs and joint angular velocities. A target work rate profile is displayed with the estimated work rate and the subject must adapt volitional muscular work to maintain the target. Physiological variables are monitored continuously.

Measurements

Cardiopulmonary response variables were monitored using a breath-by-breath system (MetaMax 3B, Cortex Biophysik GmbH, Germany). The device was calibrated prior to each test for volume and gas concentration using a 3-L syringe and a precision gas calibration mixture (15% O_2 and 5% CO_2). Heart rate was continuously measured using a chest belt (T31, Polar Electro, Finland) and recorded directly on the MetaMax system. Additionally, on the RATT, the heart rate was recorded using a receiver board (HRMI, Sparkfun, Boulder, USA). Subjects rated perceived exertion and leg fatigue every 3 minutes during the incremental exercise test using the Borg CR10 scale for dyspnea and leg fatigue (Borg, 1982;Borg, 1990).

Outcome measures

Cardiopulmonary performance parameters were evaluated as follows: VO_{2peak} was obtained from a 30-second moving average of VO_2. Peak respiratory exchange ratio (RER_{peak}) was the average value of RER during the same period. Peak heart rate (HR_{peak}) was the maximal heart rate value reached during the incremental phase. VE_{peak} was a 30-second average of the peak minute ventilation. Peak work rate (WR_{peak}) was calculated from a 10-second average of the recorded work rate. The peak Borg CR10 scale for both dyspnea and leg fatigue were those recorded at the time that subjects reached their maximal performance. Time to VO_{2peak} and the reasons for test termination were also recorded.

Statistical analysis

Data from the second test from each device were used for the comparative analysis among the three modalities. Normality of the data was assessed by the Kolmogorov-Smirnov test. Repeated measures analysis of variance (ANOVA) was conducted to determine whether there were significant differences between the peak cardiopulmonary performance parameters. If Mauchly's test of sphericity was significant ($p<0.05$), Greenhouse-Geiser corrections were used. Bonferroni post-hoc multiple comparison corrections were applied to examine the differences between each paired data set, if a significant F ratio was found.

For correlation analysis, linear regression of the VO_{2peak} and HR_{peak} values for the RATT vs cycle ergometer and the RATT vs treadmill was performed. The regression equation, the correlation coefficient (R), the coefficient of determination (R^2) and the standard error of estimate (SEE) were computed.

Test-retest reliability of VO_{2peak} and HR_{peak} on each device was analyzed using a 2-way, random intraclass correlation coefficient ($ICC_{2,1}$) and a 95% confidence interval (CI). The within-subject variation of VO_{2peak} and HR_{peak} was calculated using the coefficient of variation (Bland and Altman, 1996). The Bland and Altman limits of agreement were used to investigate the repeatability of VO_{2peak} and the HR_{peak} on each device. All analyses were performed using SPSS (Version 19.0, IBM Corp.).

3. Results

Comparison of peak values

Overall, statistically significant differences in all peak performance parameters, except in the Borg CR10 scale for leg effort, were seen between the RATT, the cycle ergometer and the treadmill (Table 1).

Absolute VO_{2peak} from the RATT, the cycle ergometer and the treadmill was (mean (SD)) 2.2 (0.56), 2.8 (0.80) and 3.2 (0.87) L/min, respectively ($p < 0.001$). Absolute VO_{2peak} obtained from the RATT was on average 19.0% lower than the cycle ergometer and 29.2% lower than on the treadmill.

HR_{peak} from the RATT, the cycle ergometer and the treadmill was 168 (9.5), 179 (7.9) and 184 (6.9) beats/min, respectively ($p < 0.001$). HR_{peak} obtained on the RATT was on average 6.0% lower than the cycle ergometer and 8.6% lower than on the treadmill.

Table 1. Peak performance values from the RATT, cycle and treadmill (n=18).

Variables	RATT	cycle ergometer	treadmill	P value
VO_{2peak} absolute (L/min)[a, b, c]	2.24 ± 0.56	2.81 ± 0.80	3.19 ± 0.87	<0.001
VO_{2peak} relative (mL/kg/min)[a, b, c]	32.3 ± 4.9	40.2 ± 7.0	45.9 ± 7.6	<0.001
HR_{peak} (beats/min)[a, b, c]	168.0 ± 9.5	178.8 ± 7.9	183.8 ± 6.9	<0.001
Percent predicted HR_{peak} (%)[a, b, c]	87.8 ± 5.3	93.5 ± 4.8	96.1 ± 4.2	<0.001
RER_{peak}[a, b]	1.03 ± 0.1	1.13 ± 0.1	1.11 ± 0.1	<0.001
VE_{peak} (L/min)[a, b, d] (n=17)	72.2 ± 21.1	101.4 ± 31.0	106.1 ± 32.0	<0.001
Borg CR10 scale dyspnea[b, d]	6.6 ± 2.0	7.6 ± 1.7	9.1 ± 0.6	<0.001
Borg CR10 scale leg effort	8. 8 ± 1.4	9.0 ± 1.6	9.1 ± 1.0	0. 65
WR_{peak} (W)[a, b, c]	65.9 ± 18.0	233.5 ± 72.7	205.9 ± 70.1	<0.001
Time to VO_{2peak} (min)	9.9 ± 1.0	9.7 ± 1.2	9.0 ± 1.1	0.063

Data are given as mean ± standard deviation. VO_2 = oxygen uptake, VO_{2peak} = peak oxygen uptake, HR_{peak} = peak heart rate, Percent predicted HR_{peak} = the peak heart rate expressed as a percentage of the predicted peak heart rate, RER_{peak} = peak respiratory exchange ratio, VE_{peak} = peak minute ventilation, WR_{peak} = peak work rate.; [a] $p < 0.001$ between the RATT and the cycle ergometer; [b] $p < 0.001$ between the RATT and the treadmill; [c] $p < 0.001$ between the cycle ergometer and the treadmill, [d] $p < 0.05$ between the cycle ergometer and the treadmill.

The three most common reasons given by the subjects for stopping the RATT test were leg fatigue (66.7%), generalized fatigue (11.1%) and leg discomfort at high work rate (11.1%). Two subjects reported foot pain due to tight foot strap fixation, which immediately resolved after the straps were released following the test. The main reasons for stopping the test on the treadmill were breathing effort (44.4%), generalized fatigue (33.3%), and leg fatigue (16.6%). The main reasons for stopping the cycle test were leg fatigue (66.7%), generalized fatigue (16.7%) and breathing effort (11.1%). No other complaints or immediate complications after the exercise testing were observed.

Correlation analysis

Linear regression analysis revealed very strong positive correlations between the RATT vs the cycle ergometer VO_{2peak} (r=0.95. p<0.001) and the RATT vs the treadmill VO_{2peak} (r=0.94. p<0.001) (Figure 2). There were strong positive correlation between the RATT HR_{peak} vs the cycle ergometer HR_{peak} (r=0.64, p<0.005) and the RATT HR_{peak} vs the treadmill HR_{peak} (r=0.62, p<0.05) (Figure 3).

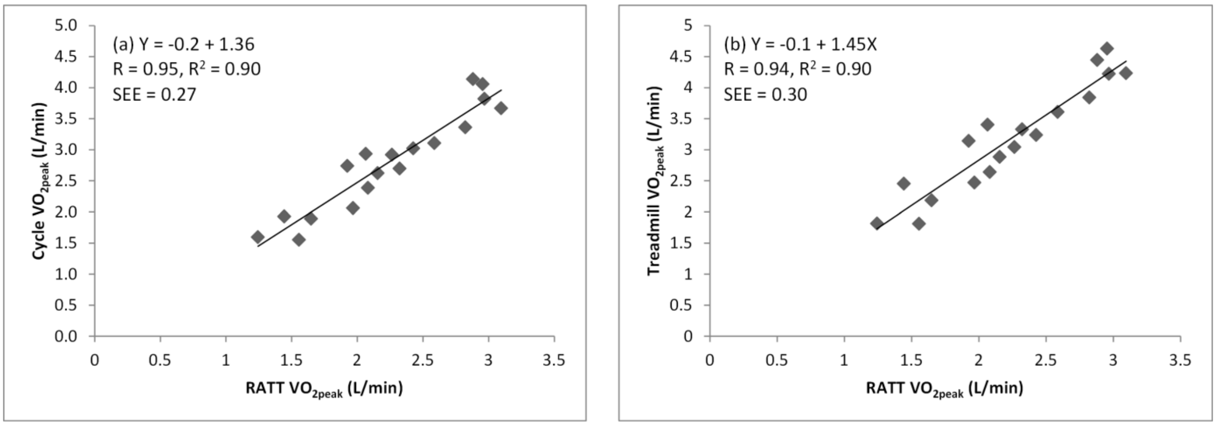

Figure 2. Linear regression analysis of VO_{2peak} (peak oxygen uptake): (a) RATT vs cycle, and (b) RATT vs treadmill. The equation, the correlation coefficient (R), the coefficient of determination (R^2) and the standard error of estimation (SEE) are shown. The regression line is shown in each graph.

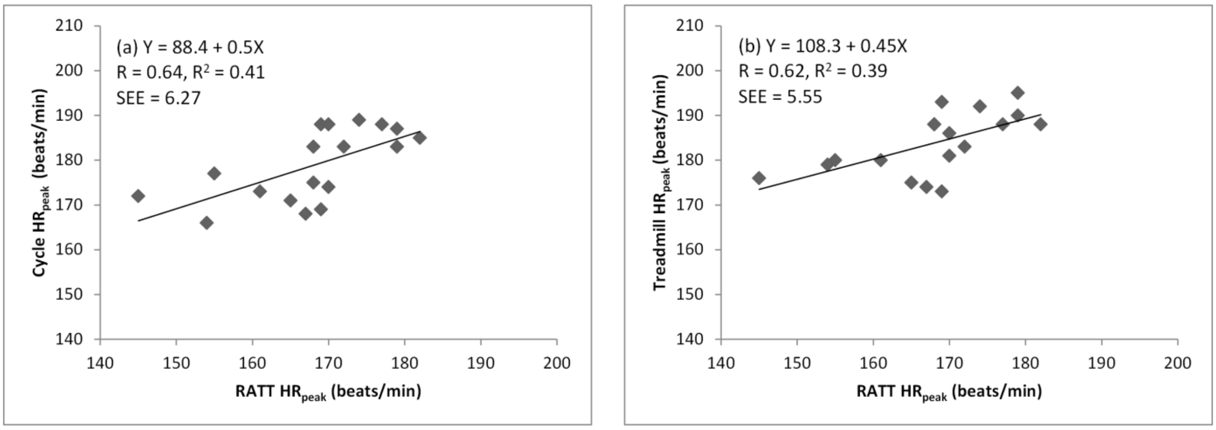

Figure 3. Linear regression analysis of HR_{peak}: (a) RATT vs cycle, and (b) RATT vs treadmill. The equation, the correlation coefficient (R), the coefficient of determination (R^2) and the standard error of estimation (SEE) are shown. The regression line is shown in each graph.

Test-retest reliability and repeatability

VO_{2peak} and HR_{peak} measured with all 3 devices had very high test-retest reliability with $ICC_{2,1} \geq 0.85$ (Table 2). The coefficient of variation of the VO_{2peak} and HR_{peak} was less than 5% in all devices. The Bland and Altman analysis showed similar limits of agreement among the devices (Table 2).

Table 2. Test-retest reliability and repeatability of each device (n=9).

	Overall mean (tests 1 and 2)	**MD (95% LoA)**	**CoV (%)**	**ICC (95% CI)**
VO_{2peak} (L/min)				
RATT	2.152	0.026 (-0.268, 0.320)	4.1	0.97 (0.89-0.99)
cycle ergometer	2.622	0.056 (-0.238, 0.342)	3.3	0.98 (0.94-1.00)
treadmill	2.924	0.013 (-0.271, 0.305)	2.4	0.99 (0.95-1.00)
HR_{peak} (beats/min)				
RATT	169.0	0.67 (12.57, -11.23)	1.8	0.89 (0.58-0.97)
cycle ergometer	180.3	2.56 (-5.77, 10.89)	1.6	0.86 (0.48-0.97)
treadmill	185.3	2.38 (-2.67, 7.33)	0.9	0.89 (0.40-0.98)

MD, mean difference; LoA, limits of agreement; CoV, coefficient of variation; ICC, intraclass correlation coefficient; CI, confidence interval; VO_{2peak}, peak oxygen uptake; HR_{peak}, peak heart rate.

4. Discussion

The aim in the present study was to compare the magnitude of peak cardiopulmonary performance parameters including oxygen uptake (VO_{2peak}) and peak heart rate (HR_{peak}) obtained from the RATT, a treadmill and a cycle ergometer. It was also an aim to assess the strength of correlations between the devices, test-retest reliability and repeatability.

The results demonstrate that VO_{2peak} on the treadmill and the cycle ergometer is higher than on the RATT. On average, the VO_{2peak} values obtained from the RATT were 81.0% of the cycle ergometer VO_{2peak} and 70.8% of the treadmill VO_{2peak}.

There were strong correlations between the RATT vs the cycle ergometer and the RATT vs the treadmill VO_{2peak}. These results are comparable to the correlation of treadmill vs total body recumbent stepper VO_{2peak} (r= 0.92) (Billinger et al., 2008a) and the correlation of arm ergometer vs treadmill VO_{2peak} (r=0.85) (Schrieks et al., 2011). Both the cycle ergometer and treadmill have been validated as standard devices for estimation of peak cardiopulmonary performance parameters. The high correlation coefficients of VO_{2peak} between the devices investigated here suggests that the RATT, similarly, is a valid device for peak exercise testing within and between subjects. There is potential for the RATT to serve as an alternative to the cycle ergometer and treadmill for the estimation of VO_{2peak} in severely impaired subjects who cannot use the standard modalities.

An alternative device for investigation of cardiopulmonary performance in impaired subjects is the supine cycle ergometer (Simonson and Wyatt, 2003). Comparing the VO_{2peak} obtained from the RATT and the published data for the supine cycle ergometer, the RATT value is lower than the supine cycle ergometer: the supine cycle ergometer was approximately 22% lower than the treadmill VO_{2peak} in normal subjects (Simonson and Wyatt, 2003). The difference in the movement pattern on the RATT may account for the lower VO_{2peak} on the RATT. However, neurological patients who have severe weakness or spasticity may have difficulty pedaling on the supine cycle ergometer because there is no leg support.

The RATT appears to be able to provoke higher VO_{2peak} compared to arm ergometry. VO_{2peak} obtained from arm ergometry in healthy subjects was 42-43% lower than the treadmill

VO_{2peak} (Schrieks et al., 2011) and 30-34% lower than the cycle ergometry VO_{2peak} (Astrand and Saltin, 1961;Reybrouck et al., 1975;Orr et al., 2013).

Regarding test-retest reliability, the ICC for VO_{2peak} from each device is high. The lower limit of the 95% CI of the ICC for each device was more than 0.75, which is considered good reliability (Lee et al., 1989;Tammemagi et al., 1995). Furthermore, the VO_{2peak} obtained from each device has high repeatability as determined by the Bland-Altman limits of agreement. The repeatability data were more precise than in a study of the repeatability of VO_{2peak} from the arm-leg ergometer as tested in healthy subjects (bias ± 1.96 SD = 0.016 ± 0.74 L/min) (Simmelink et al., 2009). The within-subject coefficients of variation for VO_{2peak} and HR_{peak} were comparable to previous studies using cycle ergometry and treadmill exercise (Garrard and Emmons, 1986;Nordrehaug et al., 1991).

HR_{peak} obtained from the RATT was lower than HR_{peak} from the treadmill and the cycle ergometer. Although strong correlations between the RATT vs cycle HR_{peak} and the RATT vs treadmill HR_{peak} were found, the correlation coefficient (R) and the coefficient of determination (R^2) are lower compared to those for VO_{2peak}. The R^2 values found in this study (0.41 for the cycle, 0.39 for the treadmill) are slightly higher than in a study of Shrieks et al. (2011), who compared a treadmill with an arm crank ergometer and found that a linear regression for HR_{peak} for treadmill vs arm crank ergometer had R^2 = 0.33, which reflects that there are some factors which influence HR_{peak} other than the effect of the device itself. Previous work showed that age explained the majority of the variance (Fairbarn et al., 1994;Tanaka et al., 2001). Other factors such as sex are controversial: Tanaka et al. (2001) stated that age predicted maximal heart rate to a large extent and that HR_{peak} is independent of gender or physical activity status; however, Faff et al. (2007) found a significant sex-dependent difference in the regression formula obtained after exercise on the treadmill and the cycle ergometer in athletes.

Repeatability of HR_{peak} from the RATT is comparable to the cycle ergometer. It was more precise compared to the study of Simmerlink et al. (2009), in which HR_{peak} repeatability from an arm-leg ergometer was 2.83 ± 19.85 beats/min. Although the point estimates of ICC of the HR_{peak} from all devices studied here were high and comparable, the 95% CI were wide. Overall, the HRpeak parameter was seen to be less reliable than VO_{2peak}.

A limitation of the present study is that, since a direct comparison between the devices in moderately or severely disabled neurological patients is not possible, it remains unknown whether the relative peak cardiopulmonary performance parameters can be extrapolated to the target patient population.

The data presented here, in particular the high correlation with standard devices and the high test-retest reliability and repeatability, support the validity of the RATT as a means of estimating peak cardiopulmonary performance parameters. The results demonstrate that the RATT has potential to be used for exercise testing in patients who have limitations for use of standard exercise testing modalities. The visual feedback system may be beneficial for the motivation of patients in both exercise testing and prescriptive exercise training. Future work should focus on the feasibility of peak cardiopulmonary performance testing using the RATT in populations with severe neurological impairments.

5. Conclusions

The present study demonstrated that VO_{2peak} from the RATT was ~20% lower than the cycle ergometer and ~30% lower than the treadmill. The magnitude of difference is less than the arm ergometer (Astrand and Saltin, 1961;Schrieks et al., 2011) but more than the supine cycle ergometer (Simonson and Wyatt, 2003). The high correlation coefficients, the high test-retest reliability and the high repeatability of the VO_{2peak} suggest that the RATT has potential to be used for exercise testing where limitations exist for use of standard modalities.

Acknowledgements

Lukas Bichsel and Matthias Schindelholz developed and implemented the force sensors, work-rate estimation algorithm and the visual feedback system for the RATT.

3.3 Submaximal cardiopulmonary thresholds on a robotics-assisted tilt table, a cycle and a treadmill: a comparative analysis

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Published as:

Saengsuwan, J., Nef, T., Laubacher, M., and Hunt, K.J. (2015) Submaximal cardiopulmonary thresholds on a robotics-assisted tilt table, a cycle and a treadmill: a comparative analysis. *Biomedical Engineering Online* 14(1)**:**104.

Abstract

Background. The robotics-assisted tilt table (RATT), including actuators for tilting and cyclical leg movement, is used for rehabilitation of severely disabled neurological patients. Following further engineering development of the system, i.e. the addition of force sensors and visual bio-feedback, patients can actively participate in exercise testing and training on the device. Peak cardiopulmonary performance parameters were previously investigated, but it also important to compare submaximal parameters with standard devices. The aim of this study was to evaluate the feasibility of the RATT for estimation of submaximal exercise thresholds by comparison with a cycle ergometer and a treadmill.

Methods. 17 healthy subjects randomly performed six maximal individualized incremental exercise tests, with two tests on each of the three exercise modalities. The ventilatory anaerobic threshold (VAT) and respiratory compensation point (RCP) were determined from breath-by-breath data.

Results. VAT and RCP on the RATT were lower than the cycle ergometer and the treadmill: oxygen uptake ($V'O_2$) at VAT was (mean (SD)) 1.2 (0.3), 1.5 (0.4) and 1.6 (0.5) L/min, respectively ($p<0.001$); $V'O_2$ at RCP was 1.7 (0.4), 2.3 (0.8) and 2.6 (0.9) L/min, respectively ($p=0.001$).

High correlations for VAT and RCP were found between the RATT vs the cycle ergometer and RATT vs the treadmill (R on the range 0.69 to 0.80). VAT and RCP demonstrated excellent test-retest reliability for all three devices (ICC from 0.81 to 0.98). Mean differences between the test and retest values on each device were close to zero.

The ventilatory equivalent for O_2 at VAT for the RATT and cycle ergometer were similar and both were higher than the treadmill. The ventilatory equivalent for CO_2 at RCP was similar for all devices. Ventilatory equivalent parameters demonstrated fair-to-excellent reliability and repeatability.

Conclusions. It is feasible to use the RATT for estimation of submaximal exercise thresholds: VAT and RCP on the RATT were lower than the cycle ergometer and the treadmill, but there were high correlations between the RATT vs the cycle ergometer and vs the treadmill. Repeatability and test-retest reliability of all submaximal threshold parameters from the RATT were comparable to those of standard devices.

1. Background

A robotics-assisted tilt table (RATT) provides safe mobilization and intensive sensorimotor stimulation for early rehabilitation of neurological patients by tilting the patient upright and implementing cyclical leg stepping movement. The RATT has separate actuators for tilting the table and for continuously moving the legs during therapy.

The RATT device employed in the present work is a clinical product (Erigo, Hocoma AG, Switzerland), which as standard includes neither measurement of the patient's work rate, nor does it provide the patient with any form of biofeedback which could be used to guide their active participation. To extend the functionality of the standard RATT, specifically to make it possible to implement formal exercise testing protocols on the device, the RATT was augmented with force sensors and a visual bio-feedback system (Bichsel et al., 2011). The force sensors were inserted under the leg cuffs which attach the patient's legs to the leg-drive systems. Using additional measurements of the moment arms and the joint angular velocities, the true work rate (in Watts) applied by the patient at the human-machine interface can be calculated in real time. The new visual biofeedback system which was added to the standard device shows the patient a target work rate and, in real time, the actual, measured work rate. The patient is instructed to adapt their volition leg effort, by producing forces into the leg cuffs in synchrony with the cyclical leg motion, in order to follow the work rate target as closely as possible. The target work rate can be chosen arbitrarily, but, for exercise testing purposes, it will be a standardized test protocol such as a constant work rate or incremental ramp. These engineering extensions have enabled severely disabled neurological patients to actively participate in exercise testing and training on the RATT (Laubacher et al., 2015;Saengsuwan et al., 2015a).

The augmented RATT device, with the engineering developments outlined above, makes possible for the first time the implementation of standardized exercise testing protocols on a robotics-assisted tilt table for determination of the key parameters of cardiopulmonary status (testing) and to allow optimized prescription of exercise regimes (training). An incremental exercise test, where the patient's work rate increases linearly over a short time period, delivers two types of parameters: (i) peak cardiopulmonary performance parameters (peak oxygen uptake and peak heart rate), which characterize aerobic capacity, and (ii) submaximal exercise thresholds (primarily the ventilatory anaerobic threshold, VAT, and respiratory compensation point, RCP), which serve mainly to allow prescription of training intensity.

We previously reported on peak cardiopulmonary performance parameters (parameter group (i), above) obtained using the augmented RATT, and compared peak responses from the augmented RATT with standard modalities (treadmill and cycle ergometers) (Saengsuwan et al., 2015b). In the present work, we investigate the second major parameter group, (ii) above, which can be obtained from incremental exercise testing, viz. the submaximal exercise thresholds VAT and RCP, together with several secondary submaximal parameters. The submaximal parameters from the RATT are directly compared with values obtained in the same subjects using treadmill and cycle ergometers. This investigation is considered clinically relevant because most neurological patients such as those with stroke or multiple sclerosis often terminate exercise testing before their maximal effort is reached. Non-cardiopulmonary factors, such as cognitive problems, muscle weakness or fatigue, are the causes linked to exercise termination in these patients (Koseoglu et al., 2006;Tang et al., 2013a).

The submaximal exercise thresholds, i.e. the oxygen uptake at the ventilatory anaerobic threshold ($V'O_{2@VAT}$) and at the respiratory compensation point ($V'O_{2@RCP}$), are important because they can provide crucial information for the assessment of fitness status (Weston and Gabbett, 2001;American Thoracic Society, 2003;Maciejczyk et al., 2014) or for exercise prescription (Meyer et al., 2005;Binder et al., 2008;Mezzani et al., 2013). They are independent of subjects' motivation (Agostoni et al., 2005) and the duration of the exercise testing protocol (Buchfuhrer et al., 1983). Furthermore, $V'O_{2@VAT}$ is reported to be useful for follow up after an intervention (Ready and Quinney, 1982;Sullivan et al., 1989;Nishijima et al., 1993), for the prediction of all-cause postoperative mortality (Wilson et al., 2010) and for the assessment of the severity of heart failure (Matsumura et al., 1983).

Other submaximal exercise parameters derived from ventilation (V'E), such as ventilatory equivalent of oxygen ($V'E/V'O_2$), ventilatory equivalent of carbon dioxide ($V'E/V'CO_2$) and the

$V'E$-vs-$V'CO_2$ slope, provide additional information regarding the existence and severity of heart and lung diseases (Wasserman et al., 1999;Sun et al., 2001). Additionally, $V'E/V'CO_2$ and the $V'E$-vs-$V'CO_2$ slope are important predictors for mortality in some groups of patients, e.g. patients with heart failure (Arena et al., 2004;Myers et al., 2009).

Numerous studies reported differences in submaximal exercise parameters on the cycle ergometer and the treadmill (Buchfuhrer et al., 1983;Sun et al., 2002;Porszasz et al., 2003;Davis et al., 2006b), the arm ergometer and the cycle ergometer (Orr et al., 2013;Loughney et al., 2014), and the arm ergometer, the cycle ergometer and the treadmill (Davis et al., 1976). It has been shown that the submaximal thresholds, e.g. $V'O_{2@VAT}$, from the arm ergometer were lower than the cycle ergometer, and $V'O_{2@VAT}$ from the cycle ergometer was lower than the treadmill (Buchfuhrer et al., 1983;Porszasz et al., 2003;Orr et al., 2013;Loughney et al., 2014). Regarding submaximal exercise parameters such as $V'E/V'CO_2$ and the $V'E$-vs-$V'CO_2$ slope, there are conflicting data. Sun et al. (2002) reported no mode-dependent difference in $V'E/V'CO_2$ and the $V'E$-vs-$V'CO_2$ slope; however, Davis et al. (2006b) found that $V'E/V'CO_2$ and the $V'E$-vs-$V'CO_2$ slope were higher on the treadmill than the cycle ergometer in women but not in men, and concluded that women demonstrated mode dependency in ventilatory efficiency indices.

Since there are no previous data regarding the comparative evaluation of submaximal exercise parameters from the RATT, the aim of this study was to evaluate the feasibility of the RATT for estimation of submaximal exercise thresholds and to compare these with the cycle ergometer and the treadmill.

2. Materials and methods

Study design and selection criteria

This descriptive study was reviewed and approved by the Ethics Review Committee of the Swiss Canton of Bern, Switzerland (Reference No. 002/12). All research subjects gave their written informed consent before participating in the study.

Subjects were included in the study if they were 18-50 years and had no history of cardiovascular, pulmonary and musculoskeletal disease that might have interfered with the exercise testing.

Testing procedures

Subjects were randomly assigned to perform six maximal individualized incremental exercise tests, with two tests on each of the three exercise modalities: a treadmill (Venus, h/p/cosmos GmbH, Germany – 2 tests), a cycle ergometer (LC7, Monark Exercise AB, Sweden – 2 tests) and a robotics-assisted tilt table (RATT; Erigo, Hocoma AG, Switzerland – 2 tests) (Saengsuwan et al., 2015b). Each test session was separated by at least 48 hours but not more than 7 days and the time of day was controlled. Subjects were advised to avoid strenuous activity for at least 24 hours and not to consume food for at least 3 hours before the exercise testing (Pina et al., 1995).

The incremental exercise testing protocol on each device was the same: it started with 3 minutes of rest, 5 minutes of warm up, 3 minutes of rest, and 3 minutes of unloaded movement before the ramp phase (Figure 1). Subjects' work rate increments during the ramp phase were estimated from their predicted maximal oxygen uptake (Jurca et al., 2005) in order that the subjects would reach their maximal exercise performance in 8-12 minutes (Buchfuhrer et al., 1983).

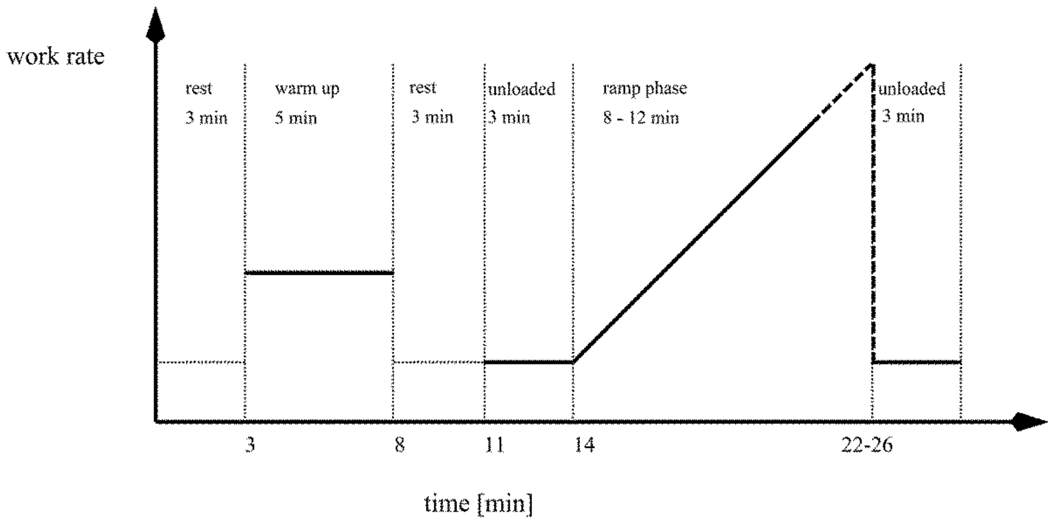

Figure 1. Incremental exercise testing protocol for all three devices.

RATT: The subjects were first secured with a body harness, thigh cuffs and foot straps. Then the RATT was tilted to 70 degrees and the stepping movement was set at 80 steps/minute, which is the maximal achievable step rate on this device. The RATT ramp rate was set in the range of 4 to 12 W/min. The subjects were instructed to actively push into the leg cuffs to produce force to follow the target work rate which they could see and compare to their actual work rate in real time (Figure 2).

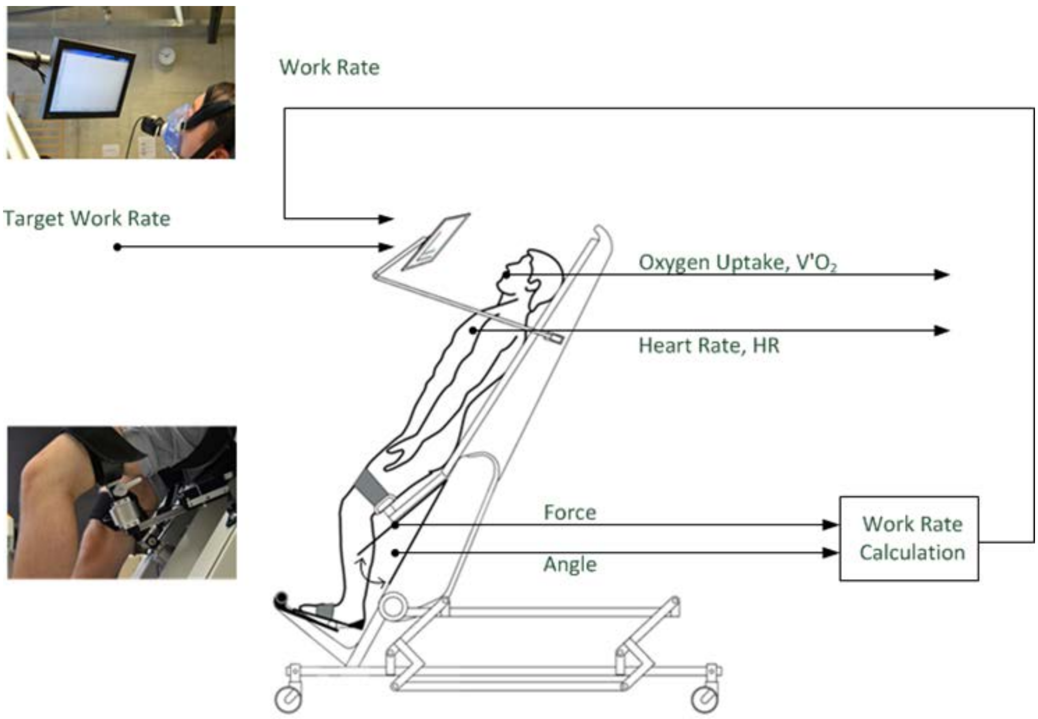

Figure 2. Robotics-assisted tilt table (RATT) with visual feedback system. The visual feedback screen shows the target work rate and the subject's work rate. The subject's work rate was calculated from the forces in the thigh cuffs and the angular velocities.

Cycle ergometer: The ramp rate ranged from 12 to 40 W/min. The settings for the seating and pedalling were adjusted for each subject and recorded to ensure the same position in subsequent tests.

Treadmill: During the ramp phase, the work rate increment ranged from 14 to 30 W/min. The work rate was increased linearly every 30 seconds using combined non-linear changes in speed and slope (Hunt, 2008).

Cardiopulmonary data were recorded with a breath-by-breath cardiopulmonary testing system (MetaMax 3B, Cortex Biophysik GmbH, Germany). Before each test, full calibration was performed: pressure calibration; volume calibration with a 3-L syringe; and two-point gas calibration using ambient air and a precision gas mixture (15% oxygen and 5% carbon dioxide). Heart rate was recorded using a chest strap (model T34, Polar Electro Oy, Finland). The cardiopulmonary variables were analysed using a 15-breath average on the corresponding Metasoft software (version 2.7.29, Cortex Biophysik GmbH, Germany) (Robergs et al., 2010).

Outcome measures

The VAT and RCP were identified according to the criteria suggested by Binder et al (2008). The VAT was visually determined using the combination of these approaches: (1) the point of deflection of $V'CO_2$ versus $V'O_2$ (V-slope method) (Beaver et al., 1986); (2) the point where $V'E/V'O_2$ reaches its minimum or starts to rise without a rise in $V'E/V'CO_2$; and, (3) the point at which partial pressure of end-tidal oxygen tension ($P_{ET}O_2$) reaches a minimum or starts to rise without a decline in the partial pressure of end-tidal carbon dioxide tension ($P_{ET}CO_2$).
The RCP was visually determined by: (1) the point of deflection of V'E versus $V'CO_2$; (2) the minimal value or nonlinear rise of $V'E/V'CO_2$; and, (3) the point that $P_{ET}CO_2$ starts to decline.
The above approaches were used to determine the values of $V'O_2$ and $V'E/V'O_2$ at VAT ($V'O_{2@VAT}$ and $V'E/V'O_{2@VAT}$), and $V'O_2$ and $V'E/V'CO_2$ at RCP ($V'O_{2@RCP}$ and $V'E/V'CO_{2@RCP}$). The slope of V'E-vs-$V'CO_2$ from the start of the ramp phase to the RCP was also estimated.

Statistical analysis

Normality of the data was assessed by the Shapiro-Wilk test. Data from the second tests on each device were used for the comparative and correlation analyses. Repeated measures analysis of variance (ANOVA) was conducted to determine whether there were differences of $V'O_{2@VAT}$ and $V'O_{2@RCP}$ between the three devices. If a statistically significant difference was found, Bonferroni post-hoc multiple comparison corrections were applied to examine differences between each paired data set.

Linear regression analysis was used to identify the correlation between the values of $V'O_{2@VAT}$ and $V'O_{2@RCP}$ on the RATT vs cycle ergometer and vs treadmill. The regression equation, correlation coefficient (R), coefficient of determination (R^2) and standard error of the estimate (SEE) were obtained.

Test-retest reliability of submaximal parameters on each device was analysed using a 2-way mixed single measures (absolute agreement) intraclass correlation coefficient ($ICC_{3,1}$) (Weir, 2005). 0.40 ≤ ICC < 0.75 was considered as fair to good reliability and ICC ≥ 0.75 was considered excellent reliability (Rosner, 2010). Repeatability was analysed using the Bland and Altman limits of agreement, incorporating mean difference and coefficient of repeatability (Bland and Altman, 1986). The within-subject coefficients of variation were also calculated (Bland and Altman, 1996). The test-retest reliability was based on only 9 subjects because of a technical problem in the measurement device detected in the data from the first tests in 8 subjects. All analyses were performed using SPSS (Version 19.0, IBM Corp.).

3. Results

Seventeen subjects were included (9 male, 8 female). The subjects had the following characteristics (mean (SD)): age 28.4 (6.4) years, height 171.8 (9.8) cm, body mass 68.1 (12.5) kg and body mass index 22.6 (2.2) kg/m^2.

VAT and RCP

The VAT was able to be identified in all subjects on all three devices. The RCP on the RATT was identified in 10 subjects (58.8%), on the cycle ergometer in 17 subjects (100%), and on the treadmill in 15 subjects (88.2%); in 9 subjects, the RCP was identified for all three devices.

The $V'O_{2@VAT}$ and $V'O_{2@RCP}$ from the RATT were lower than the cycle ergometer and the treadmill: absolute $V'O_{2@VAT}$ from the RATT, the cycle ergometer and the treadmill was (mean (SD)) 1.2 (0.3), 1.5 (0.4) and 1.6 (0.5) L/min, respectively ($p<0.001$); $V'O_{2@RCP}$ from the RATT, the cycle ergometer and the treadmill was 1.7 (0.4), 2.3 (0.8) and 2.6 (0.9) L/min, respectively ($p=0.001$) (Table 1, Figure 3). On average, the $V'O_{2@VAT}$ on the RATT was 21.4% lower than the cycle ergometer $V'O_{2@VAT}$ and 26.1% lower than the treadmill $V'O_{2@VAT}$ (mean individual differences). The $V'O_{2@RCP}$ on the RATT was 23.9% lower than the cycle ergometer $V'O_{2@RCP}$ and 30.6% lower than the treadmill $V'O_{2@RCP}$ (mean individual differences).

Table 1. Submaximal performance parameters from the RATT, cycle and treadmill (VAT: n=17; RCP: n=9).

Variables	**RATT**	**Cycle ergometer**	**Treadmill**	***p* value**
$V'O_{2peak}$ absolute (L/min) [a, b, c] (n=17)	2.39 ± 0.6	2.82 ± 0.8	3.2 ± 0.9	<0.001
Absolute $V'O_{2@VAT}$ (L/min) [a,b] (n=17)	1.16 ± 0.3	1.53 ± 0.4	1.64 ± 0.5	<0.001
Relative $V'O_{2@VAT}$ (mL/kg/min) [a,b]	17.2 ± 3.6	22.3 ± 4.0	23.8 ± 4.7	<0.001
$V'O_{2@VAT}$ as % of $V'O_{2peak}$	49.4 ± 8.8	54.5 ± 5.1	50.6 ± 5.9	0.047
HR at VAT (beats/min) [a]	114.3 ± 12.9	125.3 ± 10.6	121.7 ± 12.8	0.007
HR at VAT as percent predicted HR_{peak} (%) [a]	59.6 ± 6.3	65.4 ± 4.8	63.5 ± 5.9	0.007
Absolute $V'O_{2@RCP}$ (L/min) [a, b, c] (n=9)	1.68 ± 0.4	2.26 ± 0.8	2.55 ± 0.9	0.001
Relative $V'O_{2@RCP}$ (mL/kg/min) [a, b]	24.9 ± 5.1	33.0 ± 7.5	37.3 ± 9.3	<0.001
$V'O_{2@RCP}$ as % of $V'O_{2peak}$ [a]	68.7 ± 10.2	78.5 ± 9.9	79.1 ± 15.6	0.022
HR at RCP (beats/min) [a]	141.3 ± 17.5	153.2 ± 18.1	158.7 ± 21.9	0.004
HR at RCP as percent predicted HR_{peak} (%) [a]	73.6 ± 7.1	79.8 ± 6.9	82.6 ± 9.0	0.003
$V'E/V'O_{2@VAT}$ [b,c] (n=17)	23.6 ± 2.9	23.8 ± 3.0	21.8 ± 2.2	0.002
$V'E/V'CO_{2@RCP}$ (n=9)	28.9 ± 2.3	27.5 ± 2.8	26.7 ± 2.9	0.022
V'E-vs-$V'CO_2$ slope to RCP [a,b] (n=9)	28.4 ± 2.8	26.4 ± 2.4	25.7 ± 2.7	0.002

Data are given as mean ± standard deviation. $V'O_{2peak}$ = peak oxygen uptake, $V'O_2$ = oxygen uptake, VAT = ventilatory anaerobic threshold, $V'O_{2@VAT}$ = $V'O_2$ at VAT, HR = heart rate, HR_{peak} = peak heart rate, RCP = respiratory compensation point, $V'O_{2@RCP}$ = $V'O_2$ at RCP, $V'E/V'O_{2@VAT}$ = ventilatory equivalent of oxygen at VAT, $V'E/V'CO_{2@RCP}$ = ventilatory equivalent of carbon dioxide at RCP, V'E-vs-$V'CO_2$ slope = ventilation versus carbon dioxide output slope.

[a] $p < 0.05$ between the RATT and the cycle ergometer; [b] $p < 0.05$ between the RATT and the treadmill; [c] $p < 0.05$ between the cycle ergometer and the treadmill.

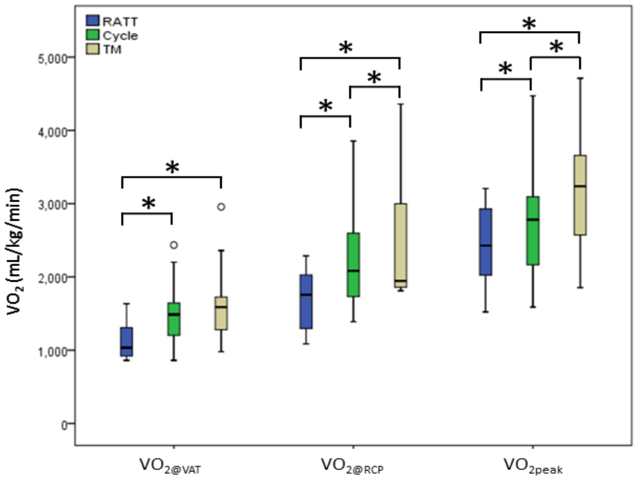

Figure 3. Box plots for $VO_{2@VAT}$, $VO_{2@RCP}$ and VO_{2peak} among the 3 devices. Asterisks represent significant differences in each paired data set assessed by Bonferroni post-hoc multiple comparison corrections.

High correlations were found between the RATT vs the cycle ergometer $V'O_{2@VAT}$ (R=0.70, p<0.01) and $V'O_{2@RCP}$ (R=0.80, p<0.01). The RATT vs the treadmill $V'O_{2@VAT}$ (R=0.73, p<0.01) and $V'O_{2@RCP}$ (R=0.69, p<0.05) demonstrated similarly high correlations (Figure 4). The $V'O_{2@VAT}$ and $V'O_{2@RCP}$ demonstrated excellent test-retest reliability for all three devices (ICC 0.81-0.98). The mean differences between the test and retest values on each device were close to zero (Table 2).

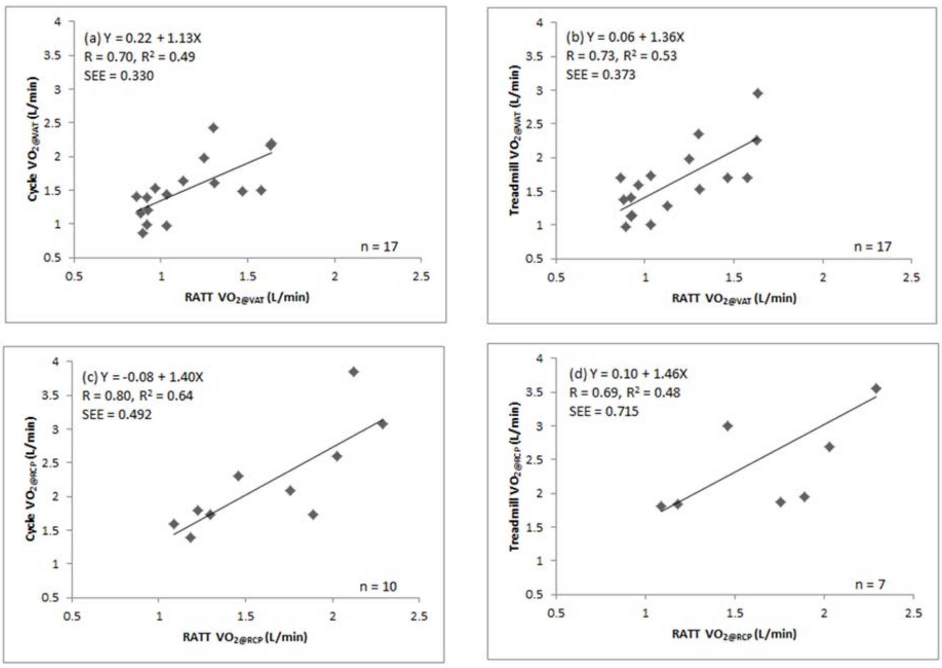

Figure 4. Linear regression analysis of $VO_{2@VAT}$ (a,b) and $VO_{2@RCP}$ (c,d) on the RATT vs the cycle ergometer and the RATT vs the treadmill.

Table 2. Test-retest reliability of the submaximal performance parameters from the RATT, cycle and treadmill.

	Overall mean (tests 1 and 2)	MD (95% LoA)	CoV (%)	ICC (95% CI)	SEM	%SEM
$V'O_{2@VAT}$ (mL/min) (n=9)						
RATT	1.129	-0.047 (-0.225, 0.131)	5.91	0.92 (0.60-0.98)	0.064	5.67
Cycle ergometer	1.411	0.082 (-0.459, 0.624)	14.10	0.81 (0.39-0.95)	0.195	13.82
Treadmill	1.561	-0.015 (-0.290, 0.259)	6.78	0.98 (0.90-1.0)	0.099	6.34
$V'O_{2@RCP}$ (L/min)						
RATT (n=6)	1.649	0.094 (-0.208, 0.395)	6.52	0.92 (0.52-0.99)	0.109	6.61
Cycle ergometer (n=8)	2.344	-0.014 (-0.706, 0.678)	8.66	0.87 (0.47-0.97)	0.245	10.45
Treadmill (n=7)	2.609	-0.069 (-0.640, 0.502)	7.17	0.95 (0.74-0.99)	0.206	7.90
$V'E/V'O_{2@VAT}$(n=9)						
RATT	23.7	-0.01 (-3.5, 3.5)	5.02	0.70 (0.10, 0.93)	1.26	5.31
Cycle ergometer	23.4	1.46 (-4.3, 7.2)	9.78	0.62 (0.05, 0.90)	2.07	8.87
Treadmill	21.7	0.20 (-2.5, 2.9)	4.33	0.74 (0.19, 0.94)	0.97	4.47
$VE/V'CO_{2@RCP}$ (L/min)						
RATT (n=6)	28.8	0.70 (-1.0, 2.4)	2.48	0.77 (0.03, 0.97)	0.62	2.16
Cycle ergometer (n=8)	27.7	1.24 (-1.2, 3.6)	4.80	0.90 (0.33, 0.98)	0.86	3.10
Treadmill (n=7)	26.4	-0.97 (-4.6, 2.6)	5.23	0.71 (0.09, 0.94)	1.30	4.92
$V'E$-vs-$V'CO_2$ slope to RCP						
RATT (n=6)	28.0	0.73 (-4.0, 5.5)	6.00	0.53 (-0.38, 0.92)	1.71	6.11
Cycle ergometer (n=8)	26.4	2.19 (-2.0, 6.4)	8.26	0.75 (0.04, 0.95)	1.52	5.77
Treadmill (n=7)	25.4	-1.14 (-4.3, 2.1)	5.13	0.74 (0.12, 0.95)	1.15	4.54

MD = mean difference, LoA = limits of agreement, CoV = coefficient of variation, ICC = intraclass correlation coefficient, CI = confidence interval, SEM = standard error of the measurement.

Other parameters

$V'E/V'O_{2@VAT}$ from the RATT and the cycle ergometer were comparable and both were higher than the treadmill. There were no significant differences in $V'E/V'CO_{2@RCP}$. The $V'E$-vs-$V'CO_2$ slope to RCP on the RATT was higher than the cycle ergometer and the treadmill (Table 1). $V'E/V'O_{2@VAT}$, $V'E/V'CO_{2@RCP}$ and $V'E$-vs-$V'CO_2$ slope to RCP had coefficients of variation less than 10%, the ICC ranged from 0.53-0.92 and the repeatability of the parameters, demonstrated by the mean difference, on the RATT and the treadmill were lower than the cycle ergometer (Table 2).

4. Discussion

The aim of this study was to evaluate the feasibility of the RATT for estimation of submaximal exercise thresholds by comparison with a cycle ergometer and a treadmill.

Submaximal exercise thresholds

We found that $V'O_{2@VAT}$ and $V'O_{2@RCP}$ were lower on the RATT than on the cycle and the treadmill. These findings are in line with the differences in $V'O_{2peak}$ found between 3 devices: the $V'O_{2peak}$ from the RATT was approximately 20% lower than the cycle $V'O_{2peak}$ and 30% lower than the treadmill $V'O_{2peak}$ (Saengsuwan et al., 2015b). The lower $V'O_2$ may be explained by the lower muscle mass needed to exercise on the RATT. Additionally, the subjects may be less familiar with the stepping movement on the RATT compared with the movement on the standard devices (Saengsuwan et al., 2015b).

High correlations were found between $V'O_{2@VAT}$ and $V'O_{2@RCP}$ on the RATT vs the treadmill and on the RATT vs the cycle ergometer; however, the correlation coefficients found were lower than those for the $V'O_{2peak}$ between devices (R=0.94-0.95) (Saengsuwan et al., 2015b). The difference in the level of correlations found may be related to differences in muscle groups and muscle fibre types used during submaximal exercise on each device for each individual (American Thoracic Society, 2003). The correlations we found for $V'O_{2@VAT}$ are higher than in studies of arm ergometer vs cycle ergometer in normal subjects (0.60-0.64) (Orr et al., 2013;Loughney et al., 2014), which may reflect the closer pattern of movement on the RATT vs the cycle ergometer compared with different muscles used for exercise on the arm ergometer.

We found no pairwise differences in $V'O_{2@VAT}$ as a percentage of $V'O_{2peak}$ among the three devices. The $V'O_{2@VAT}$ (%$V'O_{2peak}$) found here, 49-55%, is consistent with some studies on the treadmill or the cycle ergometer (range from 47-58%) (Buchfuhrer et al., 1983;Nordrehaug et al., 1991;Habedank et al., 1998;Lucia et al., 2002;Porszasz et al., 2003;Orr et al., 2013), and consistent with the observation that $V'O_{2@VAT}$ (%$V'O_{2peak}$) rarely exceeds 60% of $V'O_{2peak}$ (Meyer et al., 2005). However, other studies reported higher $V'O_{2@VAT}$ (%$V'O_{2peak}$) (range from 60.4-77%) in normal subjects (Matsumura et al., 1983;Herdy and Uhlendorf, 2011;Loe et al., 2014). The difference between $V'O_{2@VAT}$ (%$V'O_{2peak}$) among studies may be caused by the difference in methods of identifying $V'O_{2@VAT}$, the gender, the fitness level and the age distribution of the subjects studied. It was found that $V'O_{2@VAT}$ occurs at a higher percentage of $V'O_{2peak}$ in older subjects, in women and in well-trained subjects (Wasserman et al., 1999;Green et al., 2003;Meyer et al., 2005;Itoh et al., 2013).

The $V'O_{2@RCP}$ as a percentage of $V'O_{2peak}$ on the RATT was approximately 10% lower than on the treadmill. In general, data regarding $V'O_{2@RCP}$ (%$V'O_{2peak}$) are less well established compared to $V'O_{2@VAT}$ (%$V'O_{2peak}$). The $V'O_{2@RCP}$ (%$V'O_{2peak}$) identified is in accordance with previous reports (Fontana et al., 2014;Loe et al., 2014;Oussaidene et al., 2015). The lower proportion of subjects whose RCP could be identified on the RATT than the cycle or the treadmill may reflect that the RATT is less consistent in provoking cardiorespiratory loads high enough to reach RCP.

We found excellent test-retest reliability in submaximal exercise thresholds (ICC 0.81-0.98). The test-retest reliability of submaximal exercise thresholds obtained from the RATT was comparable to the treadmill and the cycle ergometer. The test-retest reliability for submaximal exercise thresholds found here were slightly lower than for peak oxygen uptake (ICC 0.97-0.99) (Saengsuwan et al., 2015b). The lower test-retest reliability in submaximal exercise thresholds than in peak oxygen uptake has been demonstrated both in normal subjects, and cardiac and pulmonary patients (Garrard and Emmons, 1986;Barron et al., 2014;Myers et al., 2015). One possible explanation is that the submaximal exercise thresholds may be more sensitive to day-to-day biological variability (Garrard and Das, 1987;Kothmann et al., 2009).

Other parameters

Although there was a trend toward higher $V'E/V'CO_{2@RCP}$ on the RATT, the pairwise comparison did not reach statistical significance. $V'E/V'O_{2@VAT}$ and $V'E$-vs-$V'CO_2$ slope to RCP on the RATT were higher than on the cycle and the treadmill. A study on the arm ergometer found significant differences in $V'E/V'O_{2@VAT}$ (27.7 and 22.1) and $V'E/V'CO_{2@VAT}$ (29.7 and

25.7) between the arm ergometer and the cycle ergometer, respectively (Orr et al., 2013). The lower ventilatory efficiency of the RATT and arm ergometer confirms that mode dependency in ventilatory efficiency indices exists. Therefore, the device used for exercise testing should be considered in the analysis of the ventilatory efficiency data. Apart from the arm ergometer, there are no data regarding the ventilatory efficiency in alternative exercise devices for a comparison of results. Most studies on alternative devices focused more on the peak cardiopulmonary values (Billinger et al., 2008a;Simmelink et al., 2009) or submaximal values of $V'O_2$ or heart rate (Saitoh et al., 2005;Bulthuis et al., 2010;Billinger et al., 2012). Since ventilatory efficiency data could provide additional information regarding the severity and prognosis of some heart or lung diseases (Wasserman et al., 1999;Sun et al., 2001;Arena et al., 2004;Myers et al., 2009), more study of these parameters on the alternative exercise testing devices should be done.

The test-retest reliability of the ventilatory efficiency was fair to excellent. The coefficient of variation was less than 10%. This is consistent with Davis et al. (2006a) who found that the test-retest reliability of the $V'E/V'CO_2$ and $V'E$-vs-$V'CO_2$ slope to RCP were high.

Our study has some limitations. Firstly, the RCP on the RATT could be identified in only 10/17 subjects. This may be because of the limitation that the RATT can elicit lower cardiopulmonary responses compared to the cycle ergometer and the treadmill in healthy subjects. Since this device is mainly intended to be used in patients with severe disability, this may not be a problem in the target population. Secondly, it cannot be verified whether the differences in submaximal exercise thresholds on each device would be the same for severely disabled neurological patients because it is not possible to implement the exercise tests on standard devices (e.g. treadmill) in severely disabled patients. Finally, the sample size was small, but the results provide preliminary estimates to support further study in target patient populations.

5. Conclusion

The results suggest that it is feasible to use the RATT for estimation of submaximal exercise thresholds: although $V'O_{2@VAT}$ and $V'O_{2@RCP}$ from the RATT were lower than the cycle ergometer and the treadmill, there were high correlations demonstrated between the RATT vs the cycle ergometer and vs the treadmill; furthermore, the repeatability and test-retest reliability of all submaximal threshold parameters from the RATT were comparable to those of standard devices. There was evidence of mode-dependent differences in $V'E/V'O_{2@VAT}$ and V'E-vs-$V'CO_2$ slope to RCP.

Abbreviations

CI: confidence interval; CoV: coefficient of variation; HR: heart rate; HR_{peak}: peak heart rate; ICC: intraclass correlation coefficient; LoA: limits of agreement; MD: mean difference; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide tension; $P_{ET}O_2$: partial pressure of end-tidal oxygen tension; R: correlation coefficient; R^2: coefficient of determination; RATT: robotics-assisted tilt table; RCP: respiratory compensation point; SEE: standard error of the estimate; SEM: standard error of measurement; VAT: ventilatory anaerobic threshold; $V'CO_2$: carbon dioxide output; V'E: minute ventilation; $V'E/V'CO_2$: ventilatory equivalent of carbon dioxide; $V'E/V'O_2$: ventilatory equivalent of oxygen; $V'O_2$: oxygen uptake; $V'O_{2peak}$: peak oxygen uptake.

Acknowledgements

Lukas Bichsel and Matthias Schindelholz developed and implemented the force sensors, work-rate estimation algorithm and the visual feedback system for the RATT.

3.4 Feasibility of cardiopulmonary exercise testing and training using a robotics-assisted tilt table in dependent-ambulatory stroke patients

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Published as:

Saengsuwan, J., Huber, C., Schreiber, J., Schuster-Amft, C., Nef, T., and Hunt, K.J. (2015). Feasibility of cardiopulmonary exercise testing and training using a robotics-assisted tilt table in dependent-ambulatory stroke patients. *Journal of NeuroEngineering and Rehabilitation* 12:88.

Abstract

Background: We evaluated the feasibility of an augmented robotics-assisted tilt table (RATT) for incremental cardiopulmonary exercise testing (CPET) and exercise training in dependent-ambulatory stroke patients.

Methods: Stroke patients (Functional Ambulation Category ≤ 3) underwent familiarization, an incremental exercise test (IET) and a constant load test (CLT) on separate days. A RATT equipped with force sensors in the thigh cuffs, a work rate estimation algorithm and real-time visual feedback to guide the exercise work rate was used. Feasibility assessment considered technical feasibility, patient tolerability, and cardiopulmonary responsiveness.

Results: Eight patients (4 female) aged 58.3 ± 9.2 years (mean ± SD) were recruited and all completed the study. For IETs, peak oxygen uptake ($V'O_{2peak}$), peak heart rate (HR_{peak}) and peak work rate (WR_{peak}) were 11.9 ± 4.0 ml/kg/min (45 % of predicted $V'O_{2max}$), 117 ± 32 beats/min (72 % of predicted HR_{max}) and 22.5 ± 13.0 W, respectively. Peak ratings of perceived exertion (RPE) were on the range "hard" to "very hard". All 8 patients reached their limit of functional capacity in terms of either their cardiopulmonary or neuromuscular performance.

A ventilatory threshold (VT) was identified in 7 patients and a respiratory compensation point (RCP) in 6 patients: mean $V'O_2$ at VT and RCP was 8.9 and 10.7 ml/kg/min, respectively, which represent 75 % (VT) and 85 % (RCP) of mean $V'O_{2peak}$. Incremental CPET provided sufficient information to satisfy the responsiveness criteria and identification of key outcomes in all 8 patients.

For CLTs, mean steady-state $V'O_2$ was 6.9 ml/kg/min (49 % of $V'O_2$ reserve), mean HR was 90 beats/min (56 % of HR_{max}), RPEs were > 2, and all patients maintained the active work rate for 10 min: these values meet recommended intensity levels for bouts of training.

Conclusions: The augmented RATT is deemed feasible for incremental cardiopulmonary exercise testing and exercise training in dependent-ambulatory stroke patients: the approach was found to be technically implementable, acceptable to the patients, and it showed substantial cardiopulmonary responsiveness. This work has clinical implications for patients with severe disability who otherwise are not able to be tested.

1. Background

Cardiopulmonary fitness is compromised in stroke patients: their peak oxygen uptake ($V'O_{2peak}$) ranges from 8-22 mL/kg/min, which corresponds to approximately half of age and gender matched healthy controls (Kelly et al., 2003;Smith et al., 2012). The low $V'O_{2peak}$ limits patients' ability to live independently (Shephard, 2009) and hinders participation in rehabilitation and exercise programmes (Billinger et al., 2014). Low cardiopulmonary fitness can further heighten the existing risk for cardiovascular disease (Bijnen et al., 1994) by predisposing patients to a sedentary lifestyle because of activity limitation and early fatigue (Tseng and Kluding, 2009).

A recent joint statement from the American Heart Association and the American Stroke Association recommends that stroke patients should undergo cardiopulmonary exercise testing (CPET) (Billinger et al., 2014). CPET delivers objective measures which allow accurate quantification of cardiorespiratory fitness, delineation of the physiological systems underlying exercise responses, and identification of exercise-limiting pathophysiological mechanisms (Guazzi et al., 2012). CPET outcomes can also be used to evaluate the effects of a longitudinal training programme and to determine the training intensity for individualized exercise prescription (Myers and Nieman, 2010;Marzolini et al., 2012;Billinger et al., 2014). However, impairments following stroke such as weakness, ataxia or spasticity can preclude some patients from exercise testing on standard devices. Semi-recumbent cycle ergometers and total-body recumbent steppers have hitherto been used as alternatives to standard treadmills and cycle ergometers in order to test patients with balance and coordination problems (Billinger et al., 2014).

Despite increasing availability of adapted devices, suitable methods and data for patients who are severely disabled are lacking. This problem is clearly demonstrated in the systematic review by Smith et al. (2012), where only 2 of the 42 studies included reported data from dependent-ambulatory patients. The authors pointed out that the exclusion of the severely disabled group may result in overestimation of cardiopulmonary fitness for the entire stroke population (Smith et al., 2012). Another systematic review on the effects of cardiovascular exercise early after stroke pointed out that concepts to influence and evaluate cardiopulmonary fitness in severely disabled patients are still lacking (Stoller et al., 2012). These open questions are addressed in the present work.

A robotics-assisted tilt table (RATT) is a device used clinically for early rehabilitation in severely impaired and bedridden neurological patients. It tilts the patient upright, provides support with a body harness, promotes weight bearing on the feet and moves the legs in a cyclic stepping movement. To promote active participation during the rehabilitation process, we have augmented a RATT system to allow patients to see their exercise work rate together with a target work rate (Bichsel et al., 2011). This approach was shown to be feasible for exercise testing both in normal subjects and in spinal cord injured patients (Saengsuwan et al., 2014;Laubacher et al., 2015). We hypothesized that the augmented RATT should enable stroke patients with severe motor weakness to be tested.

Incremental CPET aims to approach a person's limit of functional capacity in regard to cardiopulmonary and/or neuromuscular exertion. The main parameters investigated here, which can be determined from incremental CPET, include both peak and submaximal values:

- Peak: peak oxygen uptake ($V'O_{2peak}$), which represents aerobic capacity; peak heart rate (HR_{peak}); and peak work rate (WR_{peak}), which is the highest volitional effort. Additional criteria are applied to $V'O_2$ and WR responses to determine whether the observed peaks represent true maximal values.
- Submaximal: the 1st ventilatory threshold, denoted here as VT, which provides an approximation of endurance capacity (Wasserman et al., 1999;Guazzi et al., 2012); and the 2nd ventilatory threshold, denoted here as the respiratory compensation point (RCP), that occurs at the onset of hyperventilation (Meyer et al., 2004).
- Subjective measures such as rating of perceived exertion (RPE) may also be recorded at intervals throughout the test.

This is the first study where the novel augmented RATT system was applied to severely-disabled patients. Therefore we wanted to investigate whether, with this new exercise testing modality, the principal incremental CPET outcomes can be identified and whether, during constant-load CPET, sustained exercise intensity meets recommendations for training.

The aim of this study was therefore to evaluate the feasibility of the augmented RATT for incremental cardiopulmonary exercise testing and exercise training in dependent-ambulatory stroke patients, i.e. those with severe physical disability who are unable to use standard devices. Criteria for the feasibility assessment were: (i) implementation – technical feasibility of the augmented RATT for exercise testing, (ii) acceptability – was the exercise tolerable?, and (iii) responsiveness – was there a measurable, high-level cardiopulmonary reaction?

2. Materials and methods

Study design and participants

This descriptive, cross-sectional feasibility study was conducted at the Reha Rheinfelden, a rehabilitation centre in the north-west of Switzerland, from October 2013 to April 2014. The Ethics Review Committee of Canton Aargau, Switzerland, approved the study. All subjects gave their written informed consent before participating in the study.

Eight patients (4 female) aged 58.3 ± 9.2 years (mean ± SD) were recruited and all completed the study. The mean Functional Ambulation Category (FAC) was 1.8 (range 0-3; Table 1) (Holden et al., 1984). Patient inclusion criteria were: (1) a diagnosis of first-ever stroke, either ischaemic or intracerebral haemorrhage by radiologic evidence; (2) > 2 months post stroke; (3) > 18 years old; (4) dependent in ambulation with Functional Ambulation Category (FAC) ≤ 3; (5) Mini Mental State Examination (MMSE) score > 20 (cognitive function) (Folstein et al., 1975); and (6) willing to cooperate in the study and able to attend all testing sessions. Exclusion criteria were: (1) any contraindications to maximal exercise testing according to the American College of Sports Medicine guidelines (Pescatello et al., 2014); (2) any contraindications for the RATT based on guidelines from the manufacturer; (3) severe aphasia or other communication problems; and (4) severe concurrent pulmonary disease. A cardiologist reviewed all prospective subjects for cardiac status before giving approval for formal enrolment.

Table 1. Characteristics and demographic data of subjects (n=8).

Characteristic	Value
Age (years)	58.3 ± 9.2
Sex, n (%)	
Male	4 (50%)
Female	4 (50%)
Height (cm)	167.6 ± 8.8
Body mass (kg)	75.2 ± 7.4
Body mass index (kg/m^2)	26.9 ± 3.3
Type of stroke, n (%)	
Ischaemic	5 (62.5%)
Haemorrhagic	3 (37.5%)
Hemiparetic side, n (%)	
Left	4 (50%)
Right	3 (37.5%)
Bilateral	1 (12.5%)
Years post stroke, median (IQR)	1 y 42 d (8.2 y)
FAC, mean (range)	1.8 (0-3)
MMSE score	27.1 ± 3.2
Comorbidities, n (%)	
Diabetes mellitus	1 (12.5%)
Hypertension	5 (62.5%)
Dyslipidemia	2 (25%)
None	3 (37.5%)
Antihypertensive Medications, n (%)	
β-blocker	1 (12.5%)
ACE inhibitors	3 (37.5%)
Calcium channel blockers	1 (12.5%)
None	3 (37.5%)

Values are mean ± SD unless otherwise indicated.
Abbreviations: n, number; SD, standard deviation; MMSE, Mini Mental State Examination; IQR, Interquartile range; FAC, Functional Ambulation Category; ACE, angiotensin-converting-enzyme.

Robotics-assisted tilt table (RATT)

A RATT system (Erigo, Hocoma AG, Switzerland) was augmented to facilitate active participation during exercise. The basic RATT is a motorized tilt table with a body harness to support the body and two motor drives to support cyclical movement of the legs. Two thigh cuffs fix the legs and interface to the leg drives, and two foot plates support the feet. The RATT is designed to be used for early rehabilitation in neurological patients to provide early mobilization and intensive sensorimotor stimulation. Additionally, it is also claimed to enhance cardiovascular output by cyclic leg loading. During the therapy, the RATT can be tilted up from 0 to 80 degrees and the cyclic leg movement can be set to a stepping cadence between 8 and 80 steps/min.

With the augmented RATT system, patients are able to see their exercise work rate together with a target work rate (Bichsel et al., 2011). This was achieved by adding individual force sensors to the left and right leg cuffs, a work rate estimation algorithm and a real time visual feedback system (Figure 1). Patients were instructed to adapt their volitional leg effort to follow the target. Active exercise is achieved by producing forces into the leg cuffs in synchrony with the movement of the RATT.

Experimental procedures

Patients took part in three exercise sessions, each separated by a minimum of 24 hours: a familiarization, an incremental exercise test (IET), and a constant load test (CLT). Patients were instructed to avoid strenuous activity within the 24 hours before the test sessions and not to consume a large meal, caffeine or nicotine in the three hours prior to testing (Pina et al., 1995).

For each test, the patient was first transferred and secured to the RATT in accordance with the manufacturer's guidelines. Then the additional measurement systems (i.e. automatic blood pressure monitoring, and mask for breath-by-breath gas analysis) were fitted. The patient was then tilted upwards to 60 degrees. During the test, the stepping cadence was set at 80 steps/min.

The familiarization was to instruct patients regarding the RATT, the measurement systems and the test procedures. It included a short ramp phase of 5-min duration and work rate ramp of 3 W/min to allow estimation of an appropriate ramp rate for the subsequent IET.

The IET consisted of: (1) a recorded rest phase, where the patient lay passively on the RATT for 3 min; (2) a passive phase, where the RATT moved the patient's legs for 5 min; (3) a ramp phase, where the patients actively moved their legs in synchrony with the RATT motion while attempting to follow the linearly increasing work rate target. The work rate ramp was set individually in the range of 1.2 to 3.5 W/min based on observations from the ramp phase of the familiarization with the aim to bring the patient to their functional limit within 8-12 min; and (4) a recovery phase, similar to the initial passive phase, where the RATT moved the patient's legs for 5 min. The termination criteria for the ramp phase followed the American College of Sports Medicine guidelines (Pescatello et al., 2014). Additionally, blood pressure (BP) was used as a termination criterion: systolic BP > 210 mmHg or diastolic BP > 115 mmHg (Tang et al., 2006).

The CLT consisted of: (1) a rest phase for 3 min; (2) a passive phase for 5 min; (3) a constant load phase, where the patient actively moved their legs in synchrony with the RATT motion to follow the constant target work rate (the work rate was set at 40% of peak work rate (WR_{peak}) obtained from the IET) for 10 min; and (4) a recovery phase for 5 min.

Figure 1. A modified robotics-assisted tilt table (RATT) with force sensors under the thigh cuffs, visual feedback system and breath-by-breath cardiopulmonary monitoring system.

Outcome measures

Metabolic gas exchange was recorded using a breath-by-breath system (MetaMax 3B, Cortex Biophysik GmbH, Germany) and outcome variables were analysed using the associated Metasoft software. Prior to each test, pressure, volume and gas calibration were performed:

volume was calibrated using a 3-L syringe and gas was calibrated using ambient air and a certified precision gas mixture (15% oxygen and 5% carbon dioxide) according to the manufacturer's instructions. Heart rate was continuously recorded using a chest strap (model T34, Polar Electro Oy, Finland). Blood pressure was measured by automatic sphygmomanometry (HEM 907XL, Omron Corporation, USA) every 2 min during the tests.

Outcome measures for IETs were as follows. Peak oxygen uptake ($V'O_{2peak}$) was determined as the maximum of a 30-s average during the ramp phase. The peak respiratory exchange ratio (RER_{peak}) was the 30-s average of RER at the time of $V'O_{2peak}$. Peak heart rate (HR_{peak}) was defined as the highest value of HR reached during the ramp phase. The peak work rate (WR_{peak}) was calculated as the maximum of a 10-second moving average of the recorded work rate.

The first and second ventilatory thresholds (VT and RCP) were determined independently by two experienced raters (JSa and KH) using the methods described by Binder et al. (2008) and summarised in the following paragraphs, and the average of the two ratings was taken. The thresholds were characterized by the value of $V'O_2$ at the point where the criteria given below were deemed to be fulfilled. Threshold analysis was carried out visually based on 15-breath averages of the variables concerned.

The first ventilatory threshold, i.e. that which is denoted here as the VT, was determined graphically using the combination of these criteria: (1) the point at which the ventilatory equivalent for oxygen ($V'E/V'O_2$) reaches a minimum or has its first increase without a simultaneous increase in the ventilatory equivalent for carbon dioxide ($V'E/V'CO_2$); (2) the point at which partial pressure of end-tidal oxygen tension ($P_{ET}O_2$) reaches a minimum or has its first increase without a decrease in the partial pressure of end-tidal carbon dioxide tension ($P_{ET}CO_2$); and, (3) the deflection point of carbon dioxide output ($V'CO_2$) versus oxygen uptake ($V'O_2$; V-slope method). When these 3 criteria gave different results, the first two were prioritized.

The second ventilatory threshold, i.e. the respiratory compensation point (RCP), was determined graphically by inspection of: (1) the minimal value or nonlinear increase of

$V'E/V'CO_2$; (2) the turning point of $P_{ET}CO_2$; and, (3) the point of deflection of minute ventilation (V'E) versus $V'CO_2$ (Binder et al., 2008). Again, if these 3 criteria gave different results, the first two were prioritized.

Borg CR10 ratings of perceived exertion (RPE) for dyspnea and leg effort (Borg, 1982) were recorded every 3 min during the tests. The reasons for test termination were recorded.

Outcome measures for CLTs were the steady-state $V'O_2$ and heart rate during the rest, passive and constant load phases. The accuracy of the patient's achievement of target work rate was quantified by the root mean square error (RMSE) between the target and actual work rates between the first and ninth min of the constant load phase. The Borg CR10 RPE ratings for dyspnea and leg effort were recorded.

Criteria to determine feasibility of the RATT for exercise testing and training

The criteria for feasibility assessment were (Bowen et al., 2009): (i) implementation (technical feasibility of the augmented RATT for exercise testing), (ii) acceptability (was the exercise tolerable?), and (iii) responsiveness (was there a measurable, high-level cardiopulmonary reaction?).

Incremental CPET was considered to have satisfied responsiveness criteria if in a given patient at least one of the following outcomes could be identified from the IETs (adapted from Marzolini et al. (2012): $V'O_{2max}$, WR_{max}, VT or RCP.

The first two of these, $V'O_{2max}$ and WR_{max}, indicate whether a patient's functional capacity in terms of cardiopulmonary and/or neuromuscular exertion was reached:

- $V'O_{2max}$ was deemed to have been achieved if at least one of the following was observed: plateau in $V'O_2$ (increase in $V'O_2$ less than 150 mL in the final minute of exercise (MacKay-Lyons and Makrides, 2002)), RER ≥ 1.10 (or RER ≥ 1.05 for age ≥ 50 (Edvardsen et al., 2014) or $HR_{peak} \geq HR_{max} - 10$ (Marzolini et al., 2012). Here, HR_{max} was obtained from an age-related prediction formula (Pescatello et al., 2014).

- Achievement of WR_{max} was marked by a plateau in WR with the patient no longer able to reach the WR target.

Constant-load CPET was considered to have satisfied responsiveness criteria if the intensity and duration of steady-state exercise during CLTs was found to have met current recommendations for exercise and physical activity after stroke; these are defined as 40% to 70% of $V'O_2$ reserve or HR reserve; or, 55% to 80% of HR_{max}; or, RPE of 11 to 14 on the Borg scale (6-20) (Billinger et al., 2014). $V'O_2$ reserve is defined as $V'O_{2peak}$ – $V'O_{2rest}$ and HR reserve as HR_{peak} – HR_{rest} (Pescatello et al., 2014).

Statistical analysis

Descriptive statistics were used to evaluate the distribution of the variables. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as frequencies and percentages. All analyses were performed using SPSS version 19 (IBM Corporation, USA).

3. Results

(i) Implementation: The augmented RATT could be successfully used to implement both the IET and the CLT in stroke patients without the need to further modify the system. There were no technical problems that interrupted the tests.

(ii) Acceptability: The patients could understand the task to keep up with the work rate target using the visual feedback system and adaptation of their volitional leg effort. All patients could exercise until the end of the protocols without any complications. All tests were completed successfully according to the termination criteria (IET) or pre-specified duration (CLT).

(iii) Responsiveness: IET (n = 8; Table 2): Absolute $V'O_{2peak}$ was 845 ± 266 mL/min (relative $V'O_{2peak}$ was 11.9 ± 4.0 mL/kg/min), which corresponds to 45.2% of the expected $V'O_{2max}$ based on the prediction method of Wasserman et al. (1999). HR_{peak} was 117 ± 32 beats/min, which is 72.0% of the predicted value (Table 2). WR_{peak} was 22.5 ± 13.0 W. The average ratings of perceived exertion (RPE, Borg CR10) for dyspnea and leg effort at the end of the ramp phase were 5.4 and 6.6, respectively; these lie on the qualitative range of "hard" to "very hard".

Reasons for termination of the IET were: leg fatigue (n = 4, 50%); abnormal blood pressure, i.e. systolic BP > 210 mmHg, (n = 2, 25%); breathing effort (n = 1, 12.5%); and generalized fatigue (n = 1, 12.5%).

The VT was identified in 7 patients (4 female) and the RCP in 6 patients (3 female). The average absolute $V'O_2$ values at VT and RCP were 677 and 800 mL/min (relative $V'O_2$ at VT and RCP was 8.9 and 10.7 mL/kg/min) which represent 75.1% (VT) and 84.8% (RCP) of mean $V'O_{2peak}$.

Incremental CPET provided sufficient information to satisfy the responsiveness criteria, i.e. $V'O_{2max}$, WR_{max}, VT or RCP were able to be determined, in all 8 patients (4 female, 4 male): all 8 patients reached the limit of functional capacity in terms of either $V'O_{2max}$ (7 patients – 4 female) or WR_{max} (6 patients – 3 female). Of the 7 patients deemed to have satisfied the criteria for $V'O_{2max}$, 5 reached a plateau, 3 met the RER criterion and 1 met the HR_{max} criterion.

To illustrate typical IET responses, Figure 2 shows the target and measured work rates as well as cardiopulmonary responses from the IET in Patient 8. Figure 3 shows the graphical plots for determination of the VT and the RCP in the same patient.

CLT (n = 8; Table 3): The transition from passive to constant load exercise yielded a higher increase in $V'O_2$ (2.7 mL/kg/min) than did the transition from rest to passive (0.9 mL/kg/min) (Table 3). During the active phase of the exercise, all patients were able to achieve the recommended training intensity level (Billinger et al., 2014) based on percentage of $V'O_2$ reserve, percentage of HR_{max}, and RPE: the constant work rate was set at 40% of individual WR_{peak} values which resulted, on average, in a steady-state $V'O_2$ of 49 % of $V'O_2$ reserve, steady-state HR of 56 % of predicted HR_{max} and RPE > 2. All patients could maintain the active work rate for 10 min as prescribed. The accuracy of maintaining the work rate target (RMSE) was 1.3 W.

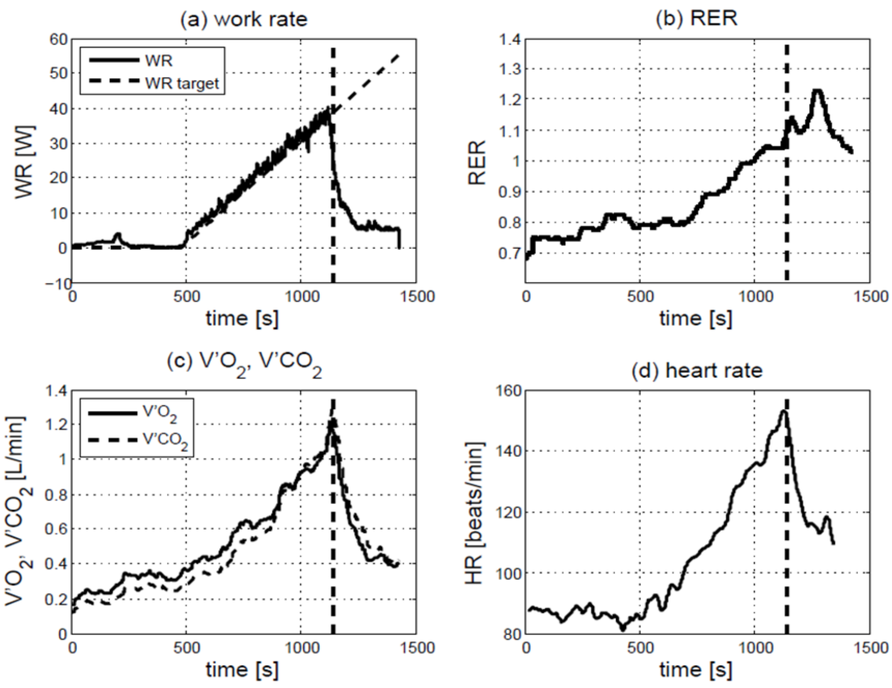

Figure 2. Typical peak cardiopulmonary responses (Subject 8) during the IET test protocol. (a) Target and measured work rates, (b) respiratory exchange ratio (RER), (c) oxygen uptake ($V'O_2$) and carbon dioxide output ($V'CO_2$), (d) heart rate (HR). The plots of RER, $V'O_2$, $V'CO_2$ and HR show averages over a 30s moving window.

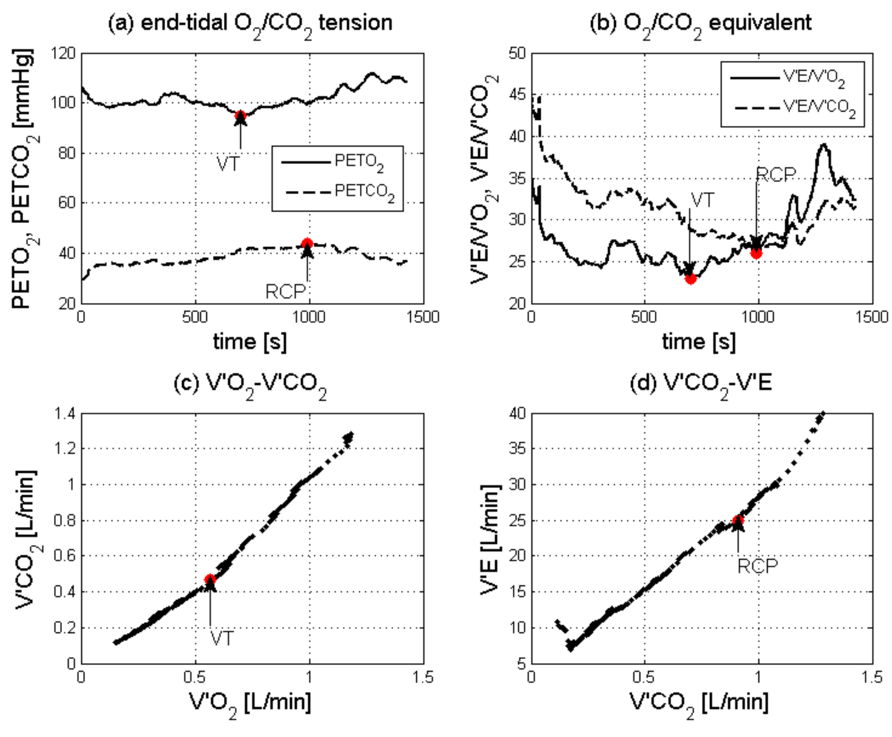

Figure 3. Determination of the 1st ventilatory threshold (VT) and the respiratory compensation point (RCP) from Subject 8. (a) VT is at the minimal value of $P_{ET}O_2$ and RCP at the turning point of $P_{ET}CO_2$, (b) VT is at the minimal value of $V'E/V'O_2$ and RCP at the minimal value of $V'E/V'CO_2$, (c) VT is at the deflection point of $V'CO_2$ vs. $V'O_2$ ('V-slope method'), (d) RCP is at the deflection point of V'E vs. $V'CO_2$.

Table 2. Summary of outcome variables from incremental exercise tests (n=8).

Outcome Variable	Value	Range
Peak Exercise Variables		
$V'O_{2peak}$ absolute (mL/min)	844.8 ± 265.7	352.0 – 1176.0
$V'O_{2peak}$ relative (mL/min/kg)	11.9 ± 4.0	5.6 – 17.5
$V'O_{2peak}$ as % of predicted $V'O_{2max}$ (Wasserman et al., 1999)	45.2 ± 8.8	32.3 – 58.2
HR_{peak} (beats/min)	117.3 ± 31.5	66.0 – 155.0
HR_{peak} as % of predicted HR_{peak} (220-age)	72.0 ± 17.7	44.9 – 99.3
SBP (mmHg)	192.9 ± 29.9	140.0 – 220.0
DBP (mmHg)	88.5 ± 12.7	78.0 – 110.0
Rate-pressure product	230.0 ± 79.8	92.4 – 341.0
RER_{peak}	1.00 ± 0.10	0.78 – 1.20
Borg CR10 RPE scale dyspnea	5.4 ± 2.8	1.0 – 9.0
Borg CR10 RPE scale leg effort	6.6 ± 1.9	4.0 – 9.0
Oxygen cost of work (mL/min/W) (n=6)	21.9 ± 3.8	16.0-26.0
WR_{peak} (W)	22.5 ± 13.0	5.5 – 38.6
Time to $V'O_{2peak}$ (sec)	742.5 ± 161.8	600.0 – 1080.0
Submaximal Exercise Variables (n=7)		
Absolute $V'O_2$ at VT (mL/min)	677.1 ± 187.1	520.0 – 1053.0
Relative $V'O_2$ at VT (mL/kg/min)	8.9 ± 2.9	6.9 – 15.0
VT as % of $V'O_{2peak}$	75.1 ± 17.6	52.3 – 100.8
RER at VT	0.88 ± 0.08	0.78 – 0.96
Absolute $V'O_2$ at RCP (mL/min) (n=6)	800.3 ± 206.7	547.0 – 1136.0
Relative $V'O_2$ at RCP (mL/kg/min) (n=6)	10.7 ± 3.1	7.3 – 16.2
RCP as % of $V'O_{2peak}$ (n=6)	84.8 ± 11.6	70.6 – 99.3
RER at RCP (n=6)	1.02 ± 0.13	0.84 – 1.24

Values are mean ± SD.

Abbreviations: $V'O_{2peak}$, peak oxygen uptake; $V'O_2$, oxygen uptake; HR, heart rate; HR_{peak}, peak heart rate; RER_{peak}, peak respiratory exchange ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPE, rating of perceived exertion; WR_{peak}, peak work rate; VT, 1st ventilatory threshold; RER, respiratory exchange ratio; RCP, respiratory compensation point.

Table 3. Summary of outcome variables from constant load tests (n=8).

Outcome Variables	Values
Initial Rest Phase	
$V'O_2$ absolute (mL/min)	243.9 ± 33.6
$V'O_2$ relative (mL/min/kg)	3.30 ± 0.43
HR (beats/min)	73.8 ± 9.8
Passive Phase	
$V'O_2$ absolute (mL/min)	316.6 ± 75.9
$V'O_2$ relative (mL/min/kg)	4.20 ± 0.78
HR (beats/min)	76.3 ± 10.0
Constant Load Phase	
$V'O_2$ absolute (mL/min)	519.5 ± 117.7
$V'O_2$ relative (mL/min/kg)	6.9 ± 1.6
$V'O_2$ as % of $V'O_2$ reserve	48.7 ± 19.1
HR (beats/min)	90.3 ± 18.6
HR as % of HR reserve	34.8 ± 32.0
HR as % of HR_{max}	56.0 ± 9.9
WR (W)	11.5 ± 6.1
Borg CR10 RPE scale dyspnea	2.1 ± 1.0
Borg CR10 RPE scale leg effort	2.9 ± 0.6
RMSE of WR (W)	1.3 ± 1.0

Values are mean ± SD.
Abbreviations: $V'O_2$, oxygen uptake; HR, heart rate; WR, work rate; W, Watts; RPE, rating of perceived exertion; RMSE, root mean square error.

4. Discussion

The aim of this study was to evaluate the feasibility of the augmented RATT for incremental cardiopulmonary exercise testing and exercise training in dependent-ambulatory stroke patients. Feasibility assessment considered technical feasibility, patient tolerability, and cardiopulmonary responsiveness.

Feasibility for incremental cardiopulmonary exercise testing

For all 8 patients tested, incremental CPET provided sufficient information to satisfy the responsiveness criteria, i.e. $V'O_{2max}$, WR_{max}, VT or RCP were successfully identified. All 8 patients also reached their limit of functional capacity due to either cardiopulmonary limitations ($V'O_{2max}$ criteria; 7 patients – 4 female) or neuromuscular limitations (WR_{max}

criteria; 6 patients – 3 female). Of these 8 patients, 5 reached both sets of criteria for cardiopulmonary and neuromuscular capacity, 2 patients satisfied only the cardiopulmonary criteria, and 1 patient reached only the neuromuscular limitation.

It is interesting that, in these numbers, female patients are at least as highly represented as males. Marzolini et al. (2012) previously noted that females after stroke were much less likely than males to achieve similar feasibility criteria from baseline CPETs: 40% for females vs. 81% for males. That difference was attributed to greater disability and weakness in the females examined in a study of mildly-impaired patients. The results herein, with severely-impaired patients, indicate that such measurement difficulties can be overcome by employing appropriate testing equipment, i.e. the augmented RATT. However, more subjects are required to reliably study these male-female ratios in the outcomes.

The $V'O_{2peak}$ reported in this study (11.9 ± 4.0 mL/kg/min) is lower than values previously reported in ambulatory stroke patients using: cycle ergometry, 17.2 ± 3.0 mL/kg/min (Eng et al., 2004); recumbent cycle ergometry, 16.0 ± 1.2 mL/kg/min (Tomczak et al., 2008); or a treadmill with body weight support, 14.4 ± 5.1 mL/kg/min (MacKay-Lyons and Makrides, 2002). This low value may be attributable in part to the more profound disability in the patients in the present study and in part to the observation that, in normal subjects, the RATT $V'O_{2peak}$ is approximately 20% lower than with a cycle ergometer and 30% lower than for a treadmill (Saengsuwan et al., 2015b).

HR_{peak} was on average 72 % of the predicted value. The rate-pressure product, which reflects the cardiovascular load during exercise, was 230. These results are comparable to previously documented results in mildly to moderately disabled stroke patients (MacKay-Lyons and Makrides, 2002;Kelly et al., 2003;Eng et al., 2004;Hyun et al., 2015). This suggests a similar myocardial work load.

Successful identification of a VT (7 patients – 4 female) and/or an RCP (6 patients – 3 female) from incremental CPET provides an additional means of prescribing exercise intensity. The relative $V'O_{2peak}$ at the VT (8.9 mL/kg/min) is lower than previous reports (Tang et al., 2006;Marzolini et al., 2012), which may be due to the same reasons as described above in relation to lower $V'O_{2peak}$. The VT as a percentage of $V'O_{2peak}$ found in this study is in line with other studies which reported values in the range 73.4 to 89.7% of $V'O_{2peak}$ (Tang et al., 2006;Chen et al., 2010;Marzolini et al., 2012).

Feasibility for exercise training

Current standards for prescription of exercise intensity for stroke patients are derived from a subset of the main incremental CPET outcomes. For stroke patients, these are (Billinger et al., 2014): 40 % to 70 % of $V'O_2$ reserve or HR reserve; or, 55 % to 80 % of maximal HR; or, RPE between 11 and 14 (6 to 20 scale), which corresponds approximately to 2 to 4.5 on the Borg CR10 RPE scale. It is recommended that this intensity level should be reached on 3 to 5 days per week using 20 to 60 min per exercise session or by multiple 10-min sessions.

The CLTs demonstrate that, during the active phase of the exercise, all patients were able to sustain the recommended intensity level based on percentage of $V'O_2$ reserve, percentage of HR_{max}, and RPE for 10 min: the constant work rate was set at 40% of individual WR_{peak} values which resulted, on average, in a steady-state $V'O_2$ of 49 % of $V'O_2$ reserve, steady-state HR of 56 % of HR_{max} and RPE > 2.

During the passive phases of the CLTs the exercise intensity was far below the recommended levels: passive $V'O_2$ was on average 18 % of $V'O_2$ reserve and passive HR was 9 % of HR reserve. This demonstrates that muscle activation is very low during passive movement and emphasises the need for active participation of the patient using the work rate biofeedback screen implemented within the augmented RATT. This low intensity of passive motion confirms a previous report with robotics-assisted treadmill exercise (Jack et al., 2011). With this low intensity, patients cannot effectively improve their cardiopulmonary fitness.

These considerations show that the augmented RATT is a feasible platform for implementation of a prescribed exercise training programme where 10-min bouts of exercise form part of the recommendations, but future work is required to investigate the response to a longitudinal training intervention using the RATT.

Limitations

The RATT $V'O_{2peak}$ was previously observed to be approximately 20% lower than the cycle ergometer and 30% lower than the treadmill in normal subjects (Saengsuwan et al., 2015b), but it is not certain whether these differences would be the same in stroke patients. Further study is needed to address the comparability of the RATT and the standard exercise testing devices (e.g. cycle ergometer) in patients who are capable of using conventional modalities.

It was observed here that the efficiency of work production on the RATT, as characterized by the inverse of the oxygen cost of the work (mean value 21.9 mL/min/W, Table 2), is substantially lower than for cycle or treadmill ergometry. This was also observed previously in able-bodied subjects on the RATT (Saengsuwan et al., 2014). This is probably due to a combination of factors including the way the muscle groups are activated and the employment of a possibly non-optimal exercise cadence. Here, a cadence of 80 steps/min was used as this is the highest rate allowed by the device employed. To improve efficiency, a higher stepping rate might be desirable, so that lower forces are needed for a given work rate target (because work rate is the product of torque and angular velocity).

The small sample size in this study may limit generalizability of the data describing cardiopulmonary fitness in dependent-ambulatory stroke patients. The $V'O_{2peak}$ in this study may still be an overestimate in relation to the overall population because we did not include patients who had heart disease or who were not approved by the cardiologist for cardiac safety. Additionally, the mean age of the patients (58.3 years) was slightly lower than the general stroke population reported in high income countries (66 years) (O'Donnell et al., 2010) or in Switzerland (72.5 years) (Michel et al., 2010).

5. Conclusion

The augmented RATT is deemed feasible for incremental cardiopulmonary exercise testing and exercise training in dependent-ambulatory stroke patients: the approach was found to be technically implementable, it was well tolerated by the patients (acceptability), and substantial cardiopulmonary responses were observed (responsiveness).

Abbreviations

CPET: cardiopulmonary exercise testing; CLT: constant load test; HR: heart rate; HR_{peak}: peak heart rate; HR_{max}: maximal heart rate; IET: incremental exercise test; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide tension; $P_{ET}O_2$: partial pressure of end-tidal oxygen tension; RATT: robotics-assisted tilt table; RCP: respiratory compensation point; RER_{peak}: peak respiratory exchange ratio; RMSE: root mean square error; RPE, rating of perceived exertion; $V'CO_2$: carbon dioxide output; V'E: minute ventilation; $V'O_2$: oxygen uptake; $V'O_{2max}$: maximal oxygen uptake; $V'O_{2peak}$: peak oxygen uptake; VT: ventilatory threshold; WR_{peak}: peak work rate.

Acknowledgements

The authors are grateful to Lukas Bichsel and Matthias Schindelholz who developed and implemented the force sensors, work-rate estimation algorithm and the visual feedback system for the RATT. We thank Marco Laubacher who assisted in protocol development and Dr Bernhard Spoendlin who did the cardiac screening. The authors gratefully acknowledge all patients for their time and motivation to participate in the study.

3.5 Test-retest reliability and four-week changes in cardiopulmonary fitness in stroke patients: evaluation using a robotics-assisted tilt table

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To be submitted

Abstract

Background: Exercise testing devices for evaluating cardiopulmonary fitness in patients with severe disability after stroke are lacking. We have adapted a robotics-assisted tilt table (RATT), which is used clinically for early neurorehabilitation, for cardiopulmonary exercise testing (CPET). Using the RATT in a sample of patients after stroke, this study aimed to investigate test-retest reliability and repeatability of CPET and to prospectively study changes in cardiopulmonary outcomes over a period of four weeks.

Methods: Stroke patients with all degrees of disability underwent 3 separate CPET sessions: 2 tests at baseline (TB1 and TB2) and 1 test at follow up (TF). TB1 and TB2 were at least 24 hours apart. TB2 and TF were 4 weeks apart. A RATT equipped with force sensors in the thigh cuffs, a work rate estimation algorithm and a real-time visual feedback system was used to guide the patients' exercise work rate during CPET. Test-retest reliability and repeatability of CPET variables were analysed using paired t-tests, the intraclass correlation coefficient (ICC), the coefficient of variation (CoV), and Bland and Altman limits of agreement. Changes in cardiopulmonary fitness during four weeks were analysed using paired t-tests.

Results: Seventeen sub-acute and chronic stroke patients (age 62.7 ± 10.4 years [mean ± SD]; 9 females) completed the test sessions. For test-retest, there were no statistically significant differences between TB1 and TB2 for most CPET variables. Absolute peak oxygen uptake, relative peak oxygen uptake, peak heart rate, peak work rate and oxygen uptake at the ventilatory anaerobic threshold and respiratory compensation point showed good to excellent test-retest reliability (ICC 0.65-0.94). For all CPET variables, CoV was 4.1-14.5%. The mean difference was close to zero in most of the CPET variables. There was no significant difference in most cardiopulmonary performance parameters during the 4-week period (TB2 vs TF).

Conclusions: These findings provide the first evidence of test-retest reliability and repeatability of the principal CPET variables using the novel RATT system and testing methodology. Good to excellent test-retest reliability and repeatability were found for all submaximal and maximal CPET variables. Reliability and repeatability of the main CPET parameters in stroke patients on the RATT were comparable to previous findings in stroke patients using standard exercise testing devices. There were no significant changes in most CPET outcomes over a period of four weeks.

1. Introduction

Stroke is one of the leading causes of adult disability worldwide (Adamson et al., 2004;Mozaffarian et al., 2015). Stroke affects not only the neurological system but also affects pulmonary and cardiovascular health (Teasell, 1992;Billinger et al., 2012). The effect of stroke on the cardiovascular system can result from: existing comorbid conditions, e.g. coronary artery disease; a direct effect of stroke on impairments in cardiovascular regulation; or, an indirect effect from weakness, fatigue or spasticity that leads to a sedentary lifestyle and results in a further decline in cardiopulmonary fitness (Myers and Nieman, 2010;Billinger et al., 2012).

Cardiopulmonary exercise testing (CPET) is important to determine a patient's cardiopulmonary fitness and to accurately prescribe an individualised exercise programme (Billinger et al., 2014). The most commonly used devices, i.e. a treadmill or a cycle ergometer, cannot be used in all stroke patients – their use is limited to mildly or moderately impaired stroke patients (Smith et al., 2012). Systematic reviews showed that suitable methods to measure cardiopulmonary fitness and to provide appropriate exercise in stroke patients with severe disability are still lacking (Stoller et al., 2012;Marsden et al., 2013). This problem needs to be addressed early because stroke incidence is projected to increase as a result of a higher proportion of older people in the population in the future (Truelsen et al., 2006) and because people who live with disability after stroke have a longer survival than formerly (Boysen et al., 2009).

A robotics-assisted tilt table (RATT), which is used clinically for early neurorehabilitation, was adapted for CPET in this study. This device was considered to have potential to be used in severely disabled patients because it has a harness to provide body support and it incorporates thigh cuffs and footplates to secure the legs. As the patient is well supported, the risk of falls or exercise related injuries is likely lower than a treadmill. The RATT was augmented with force sensors, a work rate calculation algorithm and a visual feedback system to facilitate exercise testing and training (Bichsel et al., 2011). A previous validity and reliability study in normal subjects found that peak oxygen uptake and submaximal exercise thresholds on the RATT were approximately 20% lower than for a cycle ergometer. Test-retest reliability of maximal and submaximal exercise thresholds on the RATT were comparable to standard exercise devices (Saengsuwan et al., 2015b;c). Furthermore, a feasibility study in non-ambulatory stroke patients showed that stroke patients with severe disability could successfully undergo CPET and exercise training on the RATT (Saengsuwan et al., 2015a).

Test-retest reliability of peak and submaximal cardiopulmonary exercise parameters, which are normally used as the main outcomes for exercise intervention studies, require careful analysis prior to future clinical uptake of the RATT. Although reliability data in normal subjects have been established, this form of analysis in stroke patients with various degrees of disability is still lacking.

The aims of this study were twofold: to investigate test-retest reliability and repeatability of CPET on the RATT in stroke patients with all degrees of disability; and to prospectively study changes in cardiopulmonary outcomes in this sample over a period of four weeks.

2. Methods

Study design and participants

This prospective study was approved by the Ethics Review Committee of Canton Aargau, Switzerland (Ref. EKNZ 2014-296). All subjects gave their written informed consent before participating in the study.

Sub-acute and chronic stroke patients were recruited from Reha Rheinfelden, a rehabilitation centre in the north-west of Switzerland, from December 2014 to January 2016. Patient inclusion criteria were: (1) a diagnosis of first-ever stroke, either ischaemic or intracerebral haemorrhagic; (2) ≥ 18 years old; and (3) willing to cooperate in the study and able to attend all testing sessions. Exclusion criteria were: (1) any contraindications to maximal exercise testing according to the American College of Sports Medicine guidelines (Pescatello et al., 2014); (2) any contraindications for the RATT based on guidelines from the manufacturer; (3) severe perceptual or communication problems; (4) Mini Mental State Examination (MMSE) score ≤ 17 (Folstein et al., 1975); (5) concurrent neurological diseases, e.g. Parkinson's disease; and (6) severe concurrent cardiac or pulmonary disease. A cardiologist evaluated the cardiac status of all patients before giving approval for participation.

Patients' characteristics were recorded prior to the first test: gender, age, height, body mass, body mass index (BMI), type of stroke, time of stroke diagnosis, side of weakness, comorbidity and current medication.

Study protocol

Patients underwent 3 separate CPET sessions: 2 tests at baseline (TB1 and TB2) and 1 test at follow up (TF). TB2 was conducted as soon as possible after TB1, but at least 24 hours later. TB2 and TF were 4 weeks apart. Patients were instructed to avoid strenuous activity within the 24 hours before each test session, not to consume a large meal 3 hours before, and to refrain from caffeine and nicotine 12 hours prior to testing.

Functional assessment

Prior to cardiopulmonary exercise testing, functional measures were assessed using functional ambulation category (FAC) (Holden et al., 1984), the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989) and a 6-minute walk test (6 MWT). The 6 MWT was performed indoors along a straight 50 m walking course. Standardized instructions were given to the patients according to the guidelines (ATS Committee, 2002). The six-minute walk distance (6MWD) was recorded.

Cardiopulmonary fitness assessment

Cardiopulmonary exercise testing (CPET) was performed using a robotics-assisted tilt table (RATT; model Erigo, Hocoma AG, Switzerland; Figure 1). Each test session had the same format. The patient was first transferred and secured using the body harness, thigh cuffs and foot plates according to the instruction of the manufacturer. Then, the patient was tilted upwards to 70 degrees. During the passive and incremental exercise phases, the stepping cadence was set at 80 steps/min, which is the maximal cadence allowed by the device.

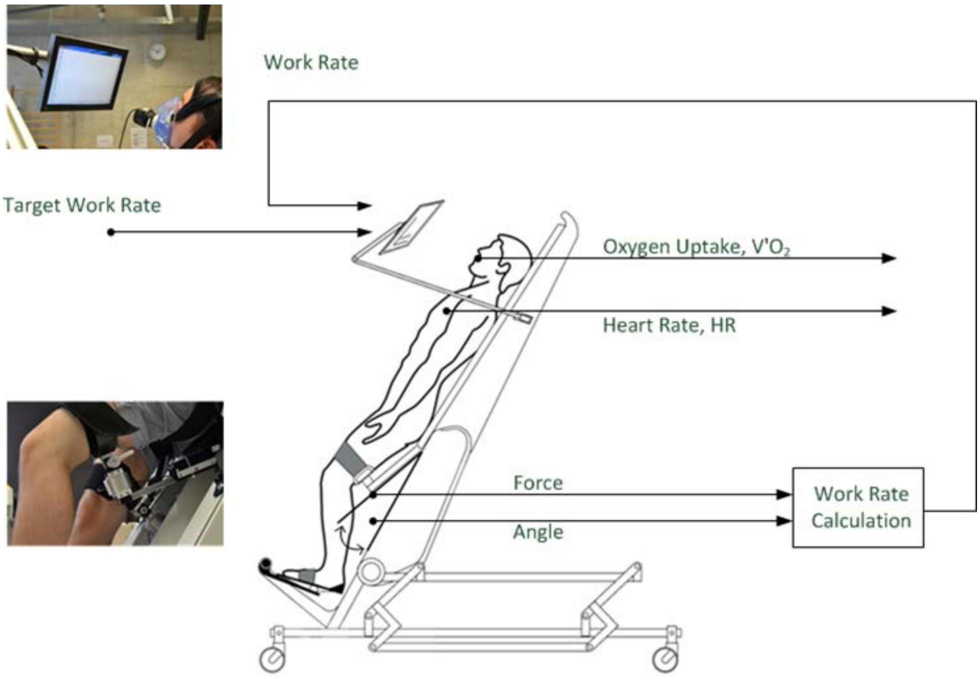

Figure 1. Robotics-assisted tilt table (RATT) with visual feedback system. The visual feedback screen shows the target work rate and the subject's work rate. The latter was calculated from the forces in the thigh cuffs and the angular velocities. Adapted from (Saengsuwan et al., 2015c).

The CPET methodology was previously described in detail elsewhere (Saengsuwan et al., 2015a) and it is briefly summarized in the following. CPET consisted of the following phases: (1) a 3-min rest phase, where the patient lay without leg movement on the RATT; (2) a passive phase, where the RATT moved the patient's legs for 5 min and the measured relative work rate was adjusted to 0 W; (3) a ramp phase, where the rate of work rate increase was in the range 1.25 to 4.5 W/min – the work rate ramp was estimated by patients' gender, age, level of weakness and comorbidity, e.g. the ramp rate for a 70 year old woman with severe disability was set to 1.25 W/min – the aim of the individualised ramp rate was to bring the patient to their maximal effort within 8-12 min of ramp onset; and (4) a recovery phase, where the patient remained passive while the RATT moved their legs for 5 min. The termination criteria for the ramp phase followed the American College of Sports Medicine guidelines (Pescatello et al., 2014). Additionally, blood pressure (BP) was used as a termination criterion: systolic BP > 210 mmHg or diastolic BP > 115 mmHg (Tang et al., 2006).

Metabolic gas exchange was recorded throughout using a breath-by-breath system (MetaMax 3B, Cortex Biophysik GmbH, Germany); the data were analysed using the associated Metasoft software. Prior to each test, standardized pressure, volume and precision gas calibration were performed according to the manufacturer's instructions. Heart rate was continuously recorded using a chest strap (model T34, Polar Electro Oy, Finland). Blood pressure was measured by manual sphygmomanometry every 2 min during the tests.

Outcome measures

The primary outcome measures were:

1. Maximal outcomes:
   - Peak oxygen uptake, denoted $V'O_{2peak}$. This was determined as the maximum of a 15-breath average during the ramp phase.
   - Peak heart rate, HR_{peak}: the highest value of HR during the ramp phase.
   - Peak respiratory exchange ratio, RER_{peak}: the 15-breath average at the time of $V'O_{2peak}$.
   - Peak work rate, WR_{peak}. This was calculated as the highest work rate achieved.
2. Submaximal outcomes:
   - Oxygen uptake at the ventilatory anaerobic threshold VAT ($V'O_{2VAT}$): the method for determination of VAT is summarized below.
   - Oxygen uptake at the respiratory compensation point RCP ($V'O_{2RCP}$), described below.

The secondary outcome measures were:

- Rating of perceived exertion (RPE) for dyspnea and leg effort at the time of peak exercise (Borg CR10) (Borg, 1990).
- Heart rate at the VAT (HR_{VAT}) and heart rate at the RCP (HR_{RCP}).
- Six-minute walk distance (6 MWD).
- The value of $V'E/V'O_2$ at VAT and $V'E/V'CO_2$ at RCP, and the slope of minute ventilation versus carbon dioxide output (V'E-vs-$V'CO_2$) from the start of the ramp phase to the RCP.

The ventilatory anaerobic threshold (VAT) and the respiratory compensation point (RCP) were determined as the averages from two independent raters (JS and LB) providing that the difference in the $V'O_2$ values of the corresponding points between two raters was less than 100 mL/min. In the case of any discrepancy, a third rater (KH) rated the point, and the VAT or RCP was the averaged data of the 2 closest values. The methods used to determine the VAT and RCP were those described by Binder et al. (2008) and summarised in the following.

The VAT was determined using the combination of these criteria: (1) the point where the ventilatory equivalent of oxygen ($V'E/V'O_2$) reaches its minimum or starts to increase without an increase in the ventilatory equivalent of carbon dioxide ($V'E/V'CO_2$); (2) the point at which the partial pressure of end-tidal oxygen tension ($P_{ET}O_2$) reaches a minimum or starts to increase without a decline in the partial pressure of end-tidal carbon dioxide tension ($P_{ET}CO_2$); and, (3) the point of deflection of $V'CO_2$ versus $V'O_2$ (V-slope method). The first two criteria were prioritized in the case that the 3 criteria gave different results.

The RCP was determined by: (1) the minimal value or nonlinear rise of $V'E/V'CO_2$; (2) the point that $P_{ET}CO_2$ starts to decline; and, (3) the point of deflection of V'E versus $V'CO_2$. Again, the first two criteria were prioritized.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as frequencies and percentages. Test-retest reliability of submaximal parameters on each device was analysed using an intraclass correlation coefficient ($ICC_{3,1}$) (Weir, 2005). For the interpretation of results, $0.40 \leq ICC < 0.75$ was considered as fair to good reliability and $ICC \geq 0.75$ was considered excellent reliability (Rosner, 2010). The within-subject coefficients of variation (CoV) were calculated (Bland and Altman, 1996).

Repeatability was analysed using the Bland and Altman limits of agreement (LoA). Heteroscedasticity was examined by calculating Pearson's correlation coefficient (r) between the absolute difference and the corresponding means. When $r>0.1$ was found, the data were considered heteroscedastic. The heteroscedastic data were log transformed using base 10 and r was recalculated. If r decreased, the data were analysed using log-transformation. The limits of agreement for heteroscedastic data were transformed back and displayed in the Bland Altman plots as a linear function $\pm b\bar{x}$ calculated by the method described by Euser et al. (2008), where $\bar{x}$ is the data mean and b is the slope of the LoA. If the data were homoscedastic, or the data were heteroscedastic but the log-transformed data did not reduce the correlation coefficient, the limits of agreement were reported as the standard mean difference (MD) ± 1.96 SD of the difference (Bland and Altman, 1986).

Two-sided paired t-tests were used to test differences between TB1 and TB2, as well as between TB2 and TF, if the difference between the tests was normally distributed (Shapiro Wilk test). Otherwise, the Wilcoxon-signed rank test was used. The significance level was set at 0.05. The analyses were performed using SPSS (Version 20.0, IBM Corp., Armonk, NY)

3. Results

General observations

Seventeen patients (9 females) aged 62.7 ± 10.4 years (mean ± SD) completed the test sessions (Table 1). Four patients were wheelchair bound, 12 patients were mildly affected and could walk independently, and one patient could walk with assistance. A further three patients were recruited but did not complete the study because of, respectively, severe hypertension, new onset atrial fibrillation, or due to automatic shutdown of the RATT caused by inappropriate forces.

Table 1. Characteristics and demographic data of subjects (n=17).

Characteristic	Value	Range
Age (years)	62.7 (10.4)	41.0-78.0
Sex, n (%)		
Male	9 (52.9%)	
Female	8 (47.1%)	
Height (cm)	169.5±6.6	160.0-183.0
Body mass (kg)	72.3±10.0	57.5-90.0
Body mass index (kg/m^2)	25.2±3.2	20.2-33.1
Type of stroke, n (%)		
Ischaemic	15 (88.2%)	
Haemorrhagic	2 (11.8%)	
Hemiparetic side, n (%)		
Left	7 (41.2%)	
Right	10 (58.8%)	
Stage, n (%)		
Sub-acute	6 (35.3%)	
Chronic	11 (64.7%)	
Days post stroke, median (IQR)	350 (788)	21-1810
FAC	3.6±2.1	0-5
NIHSS	3.1±3.2	0-11
MMSE score	28.1±2.3	21-30
Comorbidities, n (%)		
Hypertension	9 (52.9%)	
Diabetes mellitus	1 (5.9%)	
Dyslipidemia	4 (23.5%)	
None	4 (23.5%)	
Antihypertensive Medications, n (%)		
β-blocker	2 (11.9%)	
ACE inhibitors	3 (17.6%)	
Calcium channel blockers	3 (17.6%)	
None	9 (52.9%)	

Values are mean±SD unless otherwise indicated.

Abbreviations: n, number; SD, standard deviation; MMSE, Mini Mental State Examination; IQR, Interquartile range; FAC, Functional Ambulation Category; ACE, angiotensin-converting-enzyme.

There were no complications or serious adverse events. The ramp-phase duration was 8 min 53 sec ± 2 min 17 sec. Of the total of 51 completed exercise test sessions (17 patients x 3 sessions each), 49 sessions were terminated at the patient's own volition (functional capacity reached). The most common reasons for volitional exercise termination were leg fatigue (45.1%), generalized fatigue (17.6%) and inability to maintain the target work rate (15.7%). One further session was terminated because blood pressure reached the upper limit (SBP > 210 mmHg) and 1 session because of the feeling of pain from a pre-existing tension headache.

Overall, the VAT and RCP were identifiable in 49 of 51 tests (96.1%) and 40 of 51 tests (78.4%), respectively: this allowed 16 paired comparisons of $V'O_{2VAT}$ to be done for TB1 vs TB2 (test-retest) and for TB2 vs TF (four-week changes); 12 paired comparisons of $V'O_{2RCP}$ were able to be done for TB1 vs TB2 and 11 comparisons for TB2 vs TF (Tables 2 and 3). There was one measurement problem for submaximal heart rate recording in TB1, so the pairwise comparison for HR_{VAT} and HR_{RCP} were 1 pair lower than for the submaximal $V'O_2$ pairs (test-retest).

Test-retest reliability (TB1 vs TB2)

The first and second baseline tests (TB1 and TB2) were 2.1 ± 2.1 days apart. The primary outcomes ($V'O_{2peak}$, HR_{peak}, RER_{peak}, WR_{peak}, $V'O_{2VAT}$ and $V'O_{2RCP}$) showed good to excellent test-retest reliability with ICCs in the range of 0.65 to 0.94. Overall, peak exercise performance parameters showed higher reliability compared to submaximal exercise parameters: $V'O_{2peak}$ had a better reliability and repeatability shown by a higher ICC, a lower or equal coefficient of variation and a smaller mean difference (ICC 0.85, CoV 11.6%, MD 25.8 mL/min) compared to $V'O_{2VAT}$ (ICC 0.67, CoV 14.5%, MD 60.1 mL/min) and $V'O_{2RCP}$ (ICC 0.65, CoV 11.6%, MD 46.3 mL/min). Most cardiopulmonary exercise parameters were slightly higher in TB2: a statistically significant difference was found between the tests only for $V'O_{2VAT}$ (575.4 mL/min in TB1 vs 635.5 mL/min in TB2, $p = 0.045$). For the Bland and Altman analysis, the variables $V'O_{2peak}$, $V'O_{2VAT}$ and HR_{VAT} as a percentage of HR reserve were found to be heteroscedastic and the limits of agreements were calculated from the log-transformed data (Table 2, Figure 2).

Amongst the secondary outcomes, HR_{VAT}, HR_{RCP}, $V'E/V'O_2$ at VAT, $V'E/V'CO_2$ at RCP, V'E-vs-$V'CO_2$ slope and the six-minute walk distance (6 MWD) showed excellent reliability with ICC from 0.76 to 0.95 and CoV less than 6%. The only significant difference between TB1 and TB2 was for the six-minute walk test (MD 25.8 m, p=0.01). The least reliable parameters as classified by the highest CoV (28.4 and 29.5%) were the patients' subjective rating of perceived exertion (RPE), both for leg effort and dyspnea.

Changes in cardiopulmonary fitness after 4 weeks (TB2 vs TF)

The follow up test (TF) was 30.4 ± 10.2 days after the second baseline measurement (TB2). No significant changes were found in $V'O_{2peak}$, HR_{peak}, RER_{peak}, WR_{peak}, or $V'O_{2RCP}$ (Table 3), but $V'O_{2VAT}$ showed a statistically significant decrease (637.4 mL/min in TB2 vs 569.3 mL/min in TF, p=0.002). Regarding secondary outcomes, mean RPE for leg effort in TF was lower than for TB2 but the other variables were comparable (Table 3).

Table 2. Test-retest reliability of the cardiopulmonary performance parameters (n=17), unless otherwise indicated.

	TB1 (mean ± SD)	TB2 (mean ± SD)	p-value	MD	95%CI	SDD	95% LoA	CoV (%)	ICC (95% CI)
Absolute $V'O_{2peak}$ (mL/min)	1130.5±349.4	1156.4±376.6	0.60	25.8	-77.4, 129.1	200.8	-0.26x̄, 0.26x̄	11.6	0.85 (0.64, 0.94)
Relative $V'O_{2peak}$ (mL/kg/min)	15.7±4.7	16.0±4.9	0.65	0.3	-1.1, 1.7	2.8	-0.26x̄, 0.26x̄	11.6	0.84 (0.61, 0.94)
HR_{peak} (beats/min)	120.9±26.3	124.2±25.2	0.26	3.2	-2.6, 9.0	11.3	-18.9, 25.3	6.9	0.90 (0.76, 0.96)
HR_{peak}% of APMHR	78.0±15.0	80.1±13.6	0.26	2.04	-1.6, 5.7	7.2	-12.1, 16.2	6.9	0.87 (0.69, 0.95)
RER_{peak}	1.06±0.09	1.08±0.08	0.10	0.02	-0.01, 0.52	0.06	-0.1, 0.1	4.1	0.78 (0.49, 0.91)
WR_{peak} (W)	28.0±12.4	29.0±13.3	0.36	1.07	1.4, 3.5	4.6	-7.9, 10.1	13.4	0.94 (0.83, 0.98)
Absolute $V'O_{2VAT}$ (mL/min) (n=16)	575.4±105.9	635.5±177.3	0.045	60.1	-1.4, 118.9	110.2	-0.34x̄, 0.34x̄	14.5	0.67(0.27 , 0.87)
Relative $V'O_{2VAT}$ (mL/kg/min)	8.0±1.6	8.8±2.4	0.050	0.8	0.0, 1.6	1.5	-0.34x̄, 0.34x̄	14.5	0.68 (0.29, 0.88)
$V'O_{2VAT}$% of $V'O_{2peak}$ (%)	50.3±9.4	53.1±9.1	0.27	2.8	-2.4, 8.2	10	-16.8, 22.4	15.4	0.41 (-0.07, 0.74)
HR_{VAT} (beats/min) (n=15)	89.5±9.3	91.9±9.7	0.17	2.4	-1.1, 6.0	6.5	-10.3, 15.1	5.5	0.76 (0.44, 0.91)
HR_{VAT} % of HR reserve	32.6±9.2	35.1±11.5	0.33	2.5	-2.8, 7.8	9.5	-16.1, 21.1	19.5	0.58 (0.13, 0.84)
HR_{VAT} % of APMHR	57.3±5.4	58.8±5.2	0.20	1.5	-0.9, 3.8	4.3	-0.62x̄, 0.62x̄	5.5	0.67 (0.28, 0.87)
Absolute $V'O_{2RCP}$ (mL/min) (n=12)	956.5±197.9	1002.9±179.4	0.33	46.3	-54.1, 146.6	157.9	-263.2, 355.8	11.6	0.65 (0.17, 0.88)
Relative $V'O_{2RCP}$ (mL/kg/min)	13.4±2.5	14.1±2.5	0.28	0.7	-0.7, 2.1	2.1	-3.4, 4.8	11.6	0.77 (0.24, 0.87)
$V'O_{2RCP}$% of $V'O_{2peak}$ (%)	77.2±8.8	82.1±6.8	0.035	4.9	0.4, 9.5	7.1	-9.0, 18.8	8.3	0.50 (-0.02, 0.82)
HR_{RCP} (beats/min) (n=11)	112.5±18.2	113.6±17.7	0.42	1.1	-5.3, 7.4	9.4	-17.3, 19.5	5.8	0.87 (0.59, 0.96)
HR_{RCP} % of HR reserve	70.2±16.2	73.6±10.8	0.48	3.5	-7.0, 14.0	15.6	-27.1, 34.1	18.4	0.37 (-0.28, 0.78)
HR_{RCP} % of APMHR	71.3±12.1	71.9±11.7	0.72	0.7	-3.2, 4.6	5.8	-10.7, 12.1	5.8	0.89 (0.64, 0.97)
RPE dyspnea	5.1±2.0	5.2±2.7	0.93	0.1	-0.8, 0.9	1.7	-3.2, 3.4	28.4	0.76 (0.44, 0.91)
RPE leg effort	6.8±2.1	7.5±1.6	0.23	0.8	-0.3, 1.8	2	-3.1, 4.7	29.5	0.41 (-0.04, 0.73)
$V'E/V'O_2$ at VAT	31.8±4.8	32.8±5.0	0.28	0.9	-0.8, 2.7	3.3	-5.6, 7.4	7.3	0.77 (0.48, 0.91)
$V'E/V'CO_2$ at RCP	33.8±3.7	33.8±3.7	0.91	0.1	-1.2, 1.3	2.0	-3.9, 4.0	4.5	0.87 (0.60, 0.96)
$V'E$-vs-$V'CO_2$ slope to RCP	32.2±4.8	33.0±5.5	0.36	0.8	-1.0, 2.6	2.8	-4.7, 6.3	6.1	0.85 (0.58,0.96)
6 MWD (n=12)	502.5±113.4	528.3±113.1	0.010	25.8	7.5, 44.1	28.7	-30.5, 82.1	5.6	0.95 (0.65, 0.99)

TB1 = baseline test 1, TB2 = baseline test 2, APMHR = age-predicted maximal heart rate, VAT = ventilatory anaerobic threshold, RCP = respiratory compensation point, 6 MWD = 6 minute-walk distance, MD = mean difference, SDD = standard deviation of difference, LoA = limits of agreement, CoV = coefficient of variation, ICC = intraclass correlation coefficient, CI = confidence interval, x̄ = individual average.

Figure 2. Bland-Altman plots for the main outcome measures. The differences between test 2 (TB2) and test 1 (TB1) are plotted against the average values of TB1 and TB2.

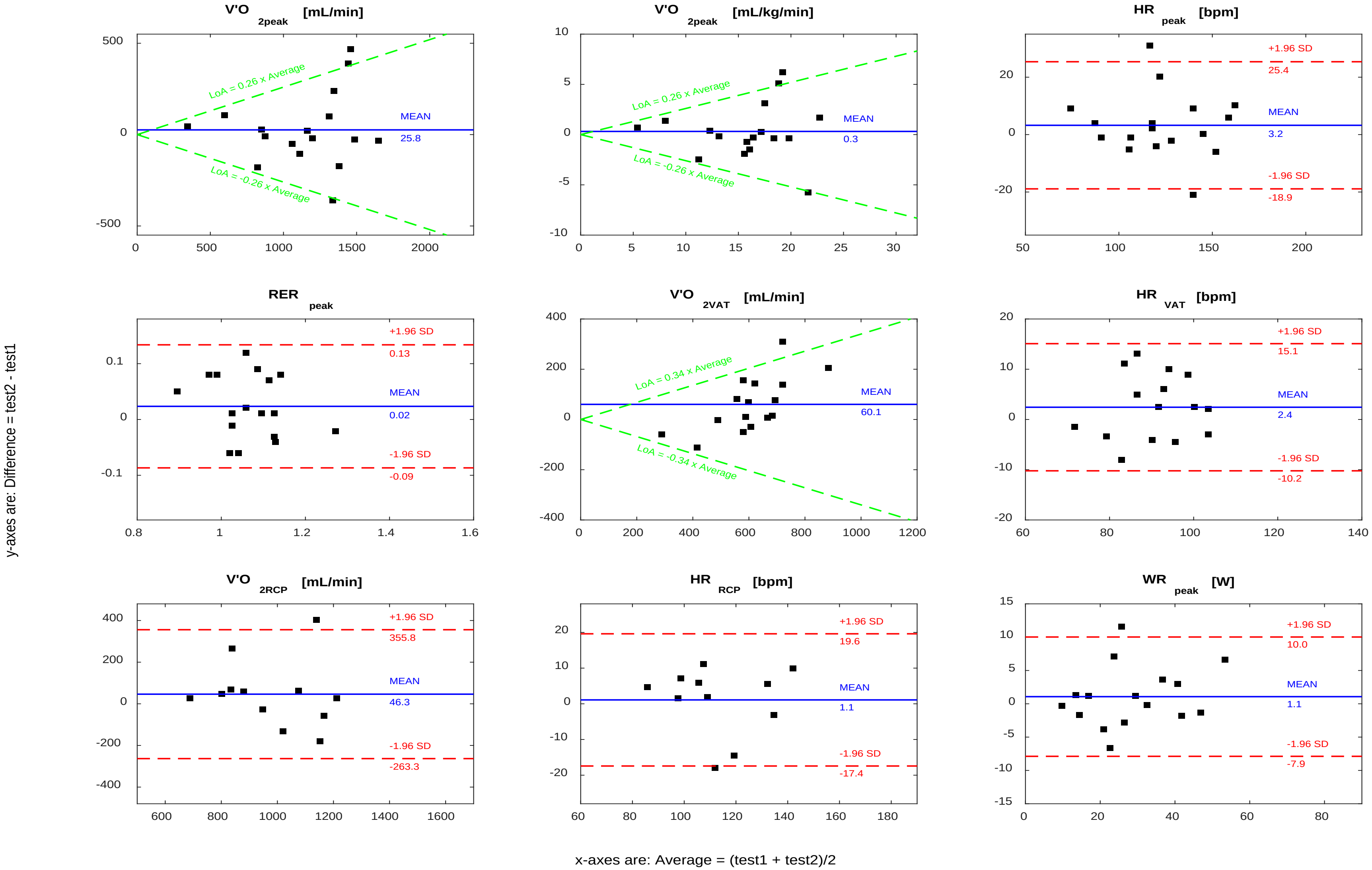

Table 3. Changes in cardiopulmonary fitness during 4 weeks (n=17), unless otherwise indicated.

	Baseline test 2 (TB2)	4-week follow up (TF)	MD (95%CI) (TF-TB2)	p-value	% changes (95%CI)
Absolute $V'O_{2peak}$ (mL/min)	1156.4±376.6	1170.0±397.5	13.6 (-102.9, 130.2)	0.81	2.8 (-6.3, 11.9)
Relative $V'O_{2peak}$ (mL/kg/min)	16.0±4.9	16.2±5.0	0.2 (-1.3, 1.6)	0.80	2.8 (-6.3, 11.9)
HR_{peak} (beats/min)	124.2±25.2	124.5±23.5	0.4 (-4.7, 5.4)	0.88	0.9 (-3.1, 5.0)
RER_{peak}	1.08±0.08	1.08±0.10	0.001 (-0.02, 0.03)	0.89	0.2 (-2.3, 2.6)
WR_{peak} (W) (n=16)	29.0±13.3	30.0±14.0	1.0 (-1.8, 3.8)	0.46	2.6 (-7.3, 12.6)
Absolute $V'O_{2VAT}$ (mL/min) (n=16)	637.4±173.3	569.3±151.3	-68.1 (-107.5, -28.7)	0.002	-9.6 (-15.1, 4.0)
Relative $V'O_{2VAT}$ (mL/kg/min)	8.8±2.3	7.9±2.0	-0.9 (-1.5, -0.4)	0.002	-9.6 (-15.1, 4.0)
HR_{VAT} (beats/min)	93.8±11.5	91.1±7.4	-2.6 (-6.8, 1.5)	0.20	-2.1 (-6.2, 2.0)
Absolute $V'O_{2RCP}$ (mL/min) (n=11)	1018.7±179.1	1055.4±199.4	36.7 (-80.4, 153.7)	0.50	4.5 (-5.9, 14.9)
Relative $V'O_{2RCP}$ (mL/kg/min)	14.2±2.5	14.7±2.5	0.5 (-1.0, 1.9)	0.48	4.5 (-5.9, 14.9)
HR_{RCP} (beats/min)	118.2±16.8	116.8±19.0	-1.3 (-8.8, 6.1)	0.69	-1.0 (-7.7, 5.7)
RPE dyspnea	5.2±2.7	4.5±1.9	-0.7 (-1.9, 0.5)	0.25	-0.7 (-25.2, 23.8)
RPE leg effort	7.5±1.6	6.1±2.2	-1.4 (-2.8, -0.2)	0.028	-16.4 (-32.4, 0.4)
$V'E/V'O_2$ at VAT (n=16)	32.4±4.6	32.4±4.2	0.1 (-1.2, 1.3)	0.93	0.5 (-3.2, 4.3)
$V'E/V'CO_2$ at RCP (n=11)	33.7±3.8	33.5±4.4	-0.1 (-1.7, 1.4)	0.86	-0.4 (-5.2, 4.5)
V'E-vs-$V'CO_2$ slope to RCP (n=11)	32.8±5.7	32.0±4.6	-0.8 (-3.4, 1.9)	0.53	-1.3 (-8.4, 5.8)
6MWD (n=12)	528.3±113.1	526.7±114.5	-1.7 (-26.1 to 22.8)	0.89	0.1 (-5.0 to 5.2)

MD = mean difference, CI = confidence interval.

4. Discussion

This study had two aims: to investigate test-retest reliability and repeatability of CPET on the RATT in stroke patients with all degrees of disability; and to prospectively study changes in cardiopulmonary outcomes in this sample over a period of four weeks.

Test-retest reliability

Good to excellent reliability was found in $V'O_{2peak}$, HR_{peak}, RER_{peak}, WR_{peak}, $V'O_{2VAT}$ and $V'O_{2RCP}$. Overall, there were slightly higher cardiopulmonary performance parameter values in test 2, but only the difference in $V'O_{2VAT}$ reached statistical significance.

The test-retest reliability of the peak cardiopulmonary exercise parameters observed here in stroke patients was lower than values seen previously in normal subjects exercising on the RATT: e.g., $V'O_{2peak}$ in normal subjects had an ICC of 0.97 and CoV 4.1% compared to ICC of 0.85 and CoV of 11.6% found in this study (Saengsuwan et al., 2015b).

Comparing the test-retest reliability results with other devices used in stroke patients is difficult as ICCs are often reported by different ICC methods. Additionally, test-retest reliability as calculated by other measures such as CoV are scarce in the stroke literature. Results from various previous studies found that $V'O_{2peak}$ obtained from a cycle ergometer, a semi-recumbent cycle ergometer, a treadmill and a robotics-assisted treadmill in both sub-acute and chronic stroke yielded excellent reliability with ICC ranging from 0.82 to 0.98 (Potempa et al., 1995;Dobrovolny et al., 2003;Duncan et al., 2003;Eng et al., 2004;Yates et al., 2004;Olivier et al., 2013;Stoller et al., 2014b). However, one study in sub-acute stroke patients using a semi-recumbent cycle ergometer showed poor reliability: there was an increase of 10% in $V'O_{2peak}$ in the second test and an ICC for $V'O_{2peak}$ of 0.50 (Tang et al., 2006); the reason for this discrepancy is unclear.

Additional maximal exercise parameters showed good to excellent test-retest reliability in previous reports. The ICC of 0.90 for HR_{peak} in the present study is comparable to previous reports (0.74 to 0.97) (Potempa et al., 1995;Dobrovolny et al., 2003;Duncan et al., 2003;Yates et al., 2004;Tang et al., 2006;Olivier et al., 2013;Stoller et al., 2014b). Similarly, ICCs for RER_{peak} and WR_{peak} of 0.78 and 0.94 found here are in line with other reports (0.72 for RER_{peak} and 0.99 for work rate) (Potempa et al., 1995;Dobrovolny et al., 2003).

For the Bland and Altman analysis, we found that $V'O_{2peak}$, $V'O_{2VAT}$ and HR_{VAT} as a percentage of HR reserve were heteroscedastic. The finding of heteroscedasticity in $V'O_{2peak}$ was also previously reported in stroke patients and patients with cardiac or pulmonary problems (Bensimhon et al., 2008;Ovando et al., 2011;Stoller et al., 2014b). This means that patients with low $V'O_{2peak}$ have lower variation in the absolute test-retest difference compared to patients with higher $V'O_{2peak}$. This finding is important as it implies that, for future studies, it would be necessary to plan the test-retest reliability protocol for specific levels of exercise capacity (i.e. $V'O_{2peak}$) to get the most accurate results because variations in the test-retest data are not uniform.

For submaximal exercise thresholds, the reliability of $V'O_{2VAT}$ and $V'O_{2RCP}$ were lower than for $V'O_{2peak}$: ICC was 0.67 and CoV was 14.5% for $V'O_{2VAT}$; ICC was 0.65 and CoV was 11.6% for $V'O_{2RCP}$. These values, again, reflect lower reliability compared to normal subjects on the same device: the ICC was 0.92 for both $V'O_{2VAT}$ and $V'O_{2RCP}$ and the CoV was 5.9% and 6.5% for $V'O_{2VAT}$ and $V'O_{2RCP}$, respectively, for normals (Saengsuwan et al., 2015c). The finding of lower reliability for $V'O_{2VAT}$ and $V'O_{2RCP}$ compared to $V'O_{2peak}$ was not unexpected as this was previously documented in normal subjects, and in heart and lung patients (Barron et al., 2014;Saengsuwan et al., 2015b;c). This was thought to be because of day-to-day biological variability, which may be related to intrinsic factors such as daily haemodynamic fluctuations (Bensimhon et al., 2008). Additionally, the lower reliability may be caused by intra and inter-rater variability for the determination of the submaximal exercise thresholds.

HR_{VAT} and HR_{RCP} were shown to have excellent reliability. These results suggest that the use of HR_{VAT} and HR_{RCP} to set the recommended intensity for exercise training could be implemented in practice. RPE showed the lowest reliability and repeatability. The findings in this respect support previous evidence that RPE is not an appropriate indicator of exercise intensity in stroke patients at a high-intensity exercise level (Sage et al., 2013). $V'E/V'O_2$ at VAT, $V'E/V'CO_2$ at RCP, and the V'E-vs-$V'CO_2$ slope showed excellent test-retest reliability with CoVs comparable to normal subjects (CoV of 4.5 to 7.3% in stroke patients vs CoV of 2.5 to 6% in normal subjects) (Saengsuwan et al., 2015c).

In summary, based on this evidence, reliability and repeatability of the main CPET parameters obtained from the RATT are comparable to previous findings reported in stroke patients using standard exercise testing devices. However, the reliability and repeatability levels found here in stroke patients were generally lower than for normal subjects on the RATT. The lower reliability may be explained by the higher variation in day-to-day levels of motivation, levels of fatigue or impaired motor control in stroke patients.

Changes in cardiopulmonary fitness after 4 weeks

Apart from $V'O_{2VAT}$, the main cardiopulmonary performance parameters did not demonstrate any statistically significant differences over the four week period. This may be because the follow up time was too short and because more than half of the patients who participated in this study were in the chronic phase following stroke. The non-significant change in mean $V'O_{2peak}$ from 16.0 to 16.2 mL/kg/min is comparable to a study in a control group of chronic stroke patients: 15.1 to 15.2 mL/kg/min in a 10-week period (Potempa et al., 1995). This reflects that without any specific exercise intervention, changes in $V'O_{2peak}$ are unlikely to be seen over a short period.

There was a significant difference (decrease) in $V'O_{2VAT}$ over the 4-week period (TB2 vs TF). However, based on the large and significant difference in $V'O_{2VAT}$ between tests TB1 and TB2 (mean difference of +60.1 mL/min) and the fact that $V'O_{2VAT}$ from TB1 was only 575.4 mL/min (Table 2), this is considered not clinically significant.

General comments

$V'O_{2peak}$ averaged over the three tests was 16 mL/kg/min. This is in line with previous reports and shows that cardiopulmonary fitness in stroke patients is low (8 to 22 mL/kg/min, 26 to 87% of age and sex-matched prediction) (Smith et al., 2012). This overall mean $V'O_{2peak}$ is 57.1% ± 14.2% of age and sex- matched predictions for a cycle ergometer (Fairbarn et al., 1994). Therefore, this comparison needs to be interpreted with caution as $V'O_{2peak}$ and $V'O_2$ at submaximal exercise thresholds are device specific: it was found that peak and submaximal $V'O_2$ were approximately 20% lower on the RATT than the cycle ergometer in normal subjects (Saengsuwan et al., 2015b;c). The low $V'O_{2peak}$ may be because of more body support provided and a difference in the movement pattern of exercise on the RATT (Saengsuwan et al., 2015b). The HR response is also device specific: the HR_{peak} of 80% of age predicted maximal heart rate (APMHR) obtained from CPET on the RATT in this study is at the lower end of the range for HR_{peak} reported for a recumbent cycle ergometer, an upright cycle ergometer and a treadmill in chronic ambulatory stroke patients (78.2 to 94.7% of APMHR) (Eng et al., 2004;Ovando et al., 2011;Marzolini et al., 2012).

An RER_{peak} of > 1.0 is a recommended criterion for maximal effort in stroke patients (van de Port et al., 2015). This criterion was satisfied here in 82.4% of all tests, although severely disabled patients were included. This is considered a high proportion compared to previous reports of only 17.6 to 62.1 % in patients with sub-acute or chronic ambulatory stroke tested on a treadmill (MacKay-Lyons and Makrides, 2002;Kelly et al., 2003;Ovando et al., 2011), 44% of sub-acute stroke patients tested on a semi-recumbent cycle ergometer (Tang et al., 2006), and 78.9% of sub-acute stroke patients using a cycle ergometer (Chen et al., 2010). These differences in the proportion of patients who achieved the criterion for maximal effort points to the importance of the device employed for CPET. Patients may experience difficulty exercising at high treadmill speed because of balance problems or fear of falling and they may have problems with leg control during cycling that prevents them from reaching their maximal exercise capacity. The RATT, in contrast, provides a body harness, thigh cuffs and foot plates to secure the patients, thus enabling them to exercise to a higher intensity.

Overall, the VAT was identified in 16/17 (94.1%) (TB1), 17/17 (100%) (TB2) and 16/17 (94.7%) (TF) patients. The RCP was identified in 13/17 (76.5%) (TB1), 14/17 (82.4%) (TB2) and 13/17 (76.5%) (TF) patients. The VAT was previously demonstrated to be identifiable in 67.3 to 83.5% of chronic stroke patients exercising on a semi-recumbent cycle ergometer, an upright cycle ergometer or a treadmill (Marzolini et al., 2012). To the best of our knowledge, there are no other studies in stroke patients that reported identification of an RCP, which is a point of substantially higher exercise intensity than the VAT, apart from our own feasibility study (Saengsuwan et al., 2015a). The finding of high proportions of patients who exercised to a sufficiently high level of intensity to allow identification of both the VAT and the RCP could be beneficial for the prescription of individualised exercise programmes (Mezzani et al., 2013).

HR_{VAT} in this study was lower than the value reported in mild to moderate chronic stroke on a treadmill: here, HR_{VAT} was approximately 59% of APMHR and in a study of Bosch et al. (2015) (n=8) it was 66% of APMHR. This difference may be due to the device specific responses to exercise as mentioned above.

Limitations

The strict patient eligibility criteria described in Methods and the exclusion of patients who had cardiac problems or who were not approved by the cardiologist for CPET led to the small sample size in this study, which may limit generalizability of the findings.

5. Conclusions

These findings provide the first evidence of test-retest reliability and repeatability of the principal CPET variables using the novel RATT system and testing methodology. Good to excellent test-retest reliability and repeatability were found for all submaximal and maximal CPET variables. Reliability and repeatability of the main CPET parameters in stroke patients on the RATT were comparable to previous findings in stroke patients using standard exercise testing devices. There were no significant changes in most cardiopulmonary exercise testing outcomes over a period of four weeks.

Abbreviations

APMHR: age-predicted maximal heart rate; CoV: coefficient of variation; CPET: cardiopulmonary exercise testing; HR: heart rate; HR_{peak}: peak heart rate; ICC: intraclass correlation coefficient; LoA: limits of agreement; MD: mean difference; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide tension; $P_{ET}O_2$: partial pressure of end-tidal oxygen tension; RATT: robotics-assisted tilt table; RCP: respiratory compensation point; RER_{peak}: peak respiratory exchange ratio; RPE, rating of perceived exertion; $V'CO_2$: carbon dioxide output; V'E: minute ventilation; $V'E/V'CO_2$: ventilatory equivalent of carbon dioxide; $V'E/V'O_2$: ventilatory equivalent of oxygen; $V'O_2$: oxygen uptake; $V'O_{2peak}$: peak oxygen uptake; VAT: ventilatory anaerobic threshold; WR_{peak}: peak work rate; 6 MWD: six-minute walk distance.

Acknowledgements

The authors are grateful to Lukas Bichsel and Matthias Schindelholz who developed and implemented the force sensors, work-rate estimation algorithm and the visual feedback system for the RATT. We thank Sophie Chen, Tanja Spycher and Sandra Küng for their help with the patient recruitment. We thank Dr Bernhard Spoendlin for cardiac screening. The authors thank all patients for their time and motivation to participate in the study.

4. General Discussion and Outlook

4.1 Recap of motivation and aim

Maximal or peak oxygen uptake ($V'O_{2max}$ or $V'O_{2peak}$) obtained from cardiopulmonary exercise testing (CPET) on a cycle ergometer or a treadmill is the gold standard measure for determining cardiopulmonary fitness (Pescatello et al., 2014). However, testing using a cycle ergometer or a treadmill is possible only in stroke patients with mild to moderate disability. In patients with severe disability after neurological insult, there are limited data regarding their cardiopulmonary fitness. Exercise testing and training in severely disabled patients is understudied (Smith et al., 2012;Stoller et al., 2012), which may be due mainly to the limitation of current devices to be used for these patients. Therefore, the aim of this PhD research was to investigate the clinical feasibility of using the augmented RATT as a method for cardiopulmonary exercise testing and training in stroke patients. The main findings of this research are summarized below.

4.2 Principal findings of this thesis

4.2.1 Cardiopulmonary performance testing using a robotics-assisted tilt table: feasibility assessment in able-bodied subjects

The first phase of the study aimed to conduct a feasibility study using the RATT for cardiopulmonary exercise testing in healthy able-bodied subjects (Chapter 3.1). For this purpose, the RATT was augmented with force sensors, a work rate calculation algorithm and a visual feedback system. The approach was found to be technically implementable and substantial cardiopulmonary responses were observed. The $V'O_{2peak}$ obtained was 20% lower than the predicted $V'O_{2peak}$ on the cycle ergometer (Wasserman et al., 1999). The lower $V'O_{2peak}$ observed may be explained by a lower level of muscle-mass recruitment during exercise on the RATT compared to standard exercise testing devices because of the body support provided and the limited range of movement available on the RATT (Saengsuwan et al., 2014).

4.2.2 Comparison of peak and submaximal cardiopulmonary performance parameters on a robotics-assisted tilt table, a cycle and a treadmill

The second phase of the study (Chapters 3.2 and 3.3) compared the peak and submaximal cardiopulmonary performance parameters achieved from the RATT, a cycle ergometer and a treadmill. Test-retest reliability of the parameters was also established. $V'O_{2peak}$, $V'O_{2VAT}$ and $V'O_{2RCP}$ on the RATT were ~20% lower than for the cycle ergometer and ~30% lower than on the treadmill. A very high correlation was found between the RATT vs the cycle ergometer $V'O_{2peak}$ ($r=0.95$, $p<0.001$) and the RATT vs the treadmill $V'O_{2peak}$ ($r=0.94$, $p<0.001$). High correlations for $V'O_{2VAT}$ and $V'O_{2RCP}$ were found between the RATT vs the cycle ergometer and the RATT vs the treadmill (r on the range 0.69 to 0.80). Additionally, test-retest reliability of the $V'O_{2peak}$, $V'O_{2VAT}$ and $V'O_{2RCP}$ obtained from the RATT was similarly high as with the standard exercise devices. These findings suggest that the RATT is a valid and reliable device for CPET. Therefore, the RATT may have potential to be used in severely impaired patients who cannot use the standard modalities (Saengsuwan et al., 2015b;c).

4.2.3 Feasibility of cardiopulmonary exercise testing and training using a robotics-assisted tilt table in dependent-ambulatory stroke patients

The next phase of the study (chapter 3.4) evaluated the feasibility of the RATT for CPET and exercise training in dependent-ambulatory stroke patients, i.e. those with severe physical disability who are unable to use standard devices. The RATT could successfully be used for both CPET and exercise training in stroke patients without the need to further modify the system. The patients could understand the task to keep up with the work rate target on the visual feedback screen by adapting their volitional leg effort. All patients could exercise until the end of the protocols without any complications. Absolute $V'O_{2peak}$ was 845 ± 266 mL/min (relative $V'O_{2peak}$ was 11.9 ± 4.0 mL/kg/min), which corresponds to 45.2% of the expected

$V'O_{2max}$ based on the prediction method of Wasserman et al. (1999). For exercise training, all patients were able to sustain exercise at the recommended intensity level based on a percentage of $V'O_2$ reserve, percentage of HR_{max}, and rate of perceived exertion (RPE) for 10 min (Billinger et al., 2014). In summary, the RATT was found to be technically implementable, it was well tolerated by the patients, and substantial cardiopulmonary responses were observed (Saengsuwan et al., 2015a). This is the first evidence to prove that the RATT can be used for CPET and exercise training in severely disabled stroke patients.

4.2.4 Test-retest reliability and four-week changes in cardiopulmonary fitness in stroke patients: evaluation using a robotics-assisted tilt table

Test-retest reliability of peak and submaximal cardiopulmonary exercise parameters, which are normally used as the main outcomes for exercise intervention studies, would be relevant for the future implementation of this device. As these data are lacking in stroke patients, the final phase of this project focused on analysing test-retest reliability and investigating changes in cardiopulmonary fitness during 4 weeks (Chapter 3.5). Good to excellent test-retest reliability (ICC 0.65-0.94, CoV 4.1-14.5%) and repeatability (mean differences close to zero) were found for most submaximal and maximal CPET variables. Overall, test-retest reliability results were comparable to standard exercise devices used for CPET in stroke patients. There were no significant differences in most CPET parameters over the period of four weeks.

In summary, the RATT is an appropriate alternative exercise testing device in patients who have limitations with standard modalities. Test-retest reliability of CPET variables was found to be comparable to standard exercise testing devices.

4.3 Clinical implications

Although CPET is recommended to be done in stroke patients in order to determine their physical fitness and to prescribe individualised exercise programmes, the implementation of CPET is still limited (Billinger et al., 2014). One of the limitations is the lack of appropriate exercise testing devices that can be used in patients with disability (Tang et al., 2009a). To the best of our knowledge, this is the first study that implemented the RATT for CPET and exercise training in stroke patients. This project provided scientific data regarding validity and reliability of CPET in both normal subjects and in stroke patients. The implementation of the RATT for CPET, on the one hand, widens the range of eligible patients as severely disabled patients can also be tested. On the other hand, it widens the application of the RATT beyond early neurorehabilitation. Additionally, the fact that severely disabled stroke patients were able to exercise on the RATT and achieved the recommended exercise intensity provides an important basis for planning exercise interventions. Currently, there are few studies which specifically focus on this aspect (Chang et al., 2012;Stoller et al., 2015). Exercise training in this group of patients to improve their cardiopulmonary fitness would have a positive impact on their daily activities and would lessen the risk of other diseases related to deconditioning, e.g. coronary artery disease (Powell et al., 1987). Numerous studies showed that higher cardiopulmonary fitness is linked with the ability to live independently (Morey et al., 1998;Paterson et al., 1999), a lower risk of all-cause mortality (Blair et al., 1996;Mora et al., 2003;Sawada et al., 2014) and lower incidence of chronic diseases such as dyslipidemia, cancer or depression (Becofsky et al., 2015;Lakoski et al., 2015;Park et al., 2015).

4.4 Limitations

Although the answer to the main aim of this research was positive, there were some unavoidable limitations in the study. First of all, it cannot be verified whether the observed differences in peak and submaximal exercise parameters on each device (the RATT, the cycle ergometer and the treadmill) would be the same for severely disabled neurological patients because it is not possible to carry out the exercise tests on standard devices (e.g. treadmill) in severely disabled patients. Secondly, although we tried to make the data more generalizable by including both sub-acute and chronic stroke patients as well as including patients with all degrees of disability, the patients who participated in our study did not necessarily represent stroke patients in the general population. The patients enrolled in the study were younger (mean age of 62.7 years) than in other reports (mean age of 66.0-72.5 years) (Michel et al., 2010;O'Donnell et al., 2010). Participants were screened and approved by a cardiologist for cardiac safety and, as a result, our sample may be healthier than stroke patients in general. Additionally, they may be more motivated than their non-participating peers. Thirdly, because of time limitations, we had a rather small sample size for test-retest reliability analysis. However, as most studies of test-retest reliability in stroke patients had sample sizes of 9 to 53 (Potempa et al., 1995;Dobrovolny et al., 2003;Duncan et al., 2003;Eng et al., 2004;Yates et al., 2004;Tang et al., 2006;Olivier et al., 2013;Stoller et al., 2014b), we consider the sample size used in this study to be realistic and to provide valid preliminary data.

4.5 Future directions

As the RATT is a novel device in the context of exercise testing and training, several open questions remain. In order to effectively implement the RATT for exercise testing, a method to predict the optimal work rate increment for each patient that will bring the patient to their maximal exercise capacity in the desired duration of 8-12 min should be developed (Buchfuhrer et al., 1983). Moreover, the optimal cadence for CPET should be examined. Although the cadence used in this project was 80 steps/min (the highest rate possible on the RATT), it is not known what would be the most appropriate cadence for exercise testing and training in this group of patients.

For exercise training, the next logical approach is to evaluate the effect of an individualised exercise intervention in early sub-acute or chronic stroke patients who are severely disabled. Future research will also need to focus on the most appropriate methods to implement exercise training in stroke patients, e.g. continuous mild-moderate intensity training or interval training.

5. References

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6. Acknowledgements

I would like to take this opportunity to thank all the people who accompanied or supported me during my PhD study.

Prof. Dr. sc. Tobias Nef, my supervisor, who gave me the opportunity to do the PhD study in the Gerontechnology and Rehabilitation group, I would like to sincerely thank for his support during the whole duration of my PhD study.

I would like to express my sincere gratitude to Prof. Dr. Kenneth J. Hunt, my co-advisor, for his guidance and support through the project. Thank you for giving me the opportunity to work on this topic. His guidance helped me throughout the research and thesis writing. I would like to thank Prof. Dr. med. Urs Mosimann for accepting the role of co-referee and for supporting me during my PhD study.

My sincere thanks to Prof. Dr. med. Thierry Ettlin and Dr. Corina Schuster-Amft who gave me an opportunity to do the research in Reha Rheinfelden. I would like to thank Zorica Suica and Michael McCaskey for their help with the patient recruitment and contact.

A special thanks to Prof. Dr. med. Matthias Wilhelm and Dr. med. Lukas Trachsel for giving me an opportunity to observe the cardiopulmonary exercise testing in the Inselspital and for useful comments about the project.

I thank former and present group members of the Institute for Rehabilitation and Performance Technology and the Gerontechnology and Rehabilitation Group for scientific discussions and for their friendliness. A special thanks to Marco Laubacher, Matthias Schindelholz, Oliver Stoller, and Lukas Bichsel for helping with the protocol development and for technical support. I especially thank Juan Fang who helped me through the adjustment period of my study. Furthermore, I would like to give a special thanks to the master students: Cèline Huber, Jonathan Schreiber, Sophie Chen, Tanja Spycher, Lucia Berger and Sandra Küng for their help in recruiting the patients and during the testing procedure. I would like to give my special thanks to Nicole Gruber, Rahel Bieri, Prabitha Urwyler and Giuseppe Zito for their help whenever I had questions regarding the PhD study.

I gratefully acknowledge Bern University of Applied Sciences for financial support during my study and the Graduate School of Health Sciences for offering interesting courses and for financially supporting participation in a congress.

I would like to thank my friends Apiradee Nicharat, Suwanwadee Thaiwichai, Issarawan Taoyuwapan, Wanlapa Assawabenjang, Sirachat Vidyakorn, and Patpiya Sirasaporn for their support and visit during my study.

I am grateful for the support of my family and friends throughout my PhD study. I would like to express my sincere gratitude to my Mum and Dad for their love and encouragement.

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8. List of Publications

Journal Articles

Saengsuwan, J., Berger, L., Schuster-Amft, C., Nef, T., and Hunt, K.J. (2016). Test-retest reliability and four-week changes in cardiopulmonary fitness in stroke patients: evaluation using a robotics-assisted tilt table. To be submitted.

Saengsuwan, J., Nef, T., and Hunt, K.J. (2016). A method for predicting peak work rate for cycle ergometer and treadmill ramp tests. *Clinical Physiology and Functional Imaging*. Epub 2016 Jan 12.

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Saengsuwan, J., Huber, C., Schreiber, J., Schuster-Amft, C., Laubacher, M., Nef, T., and Hunt, K.J. (2015). Assessment of the gas exchange threshold and respiratory compensatory point in dependent-ambulatory stroke patients using a robotics-assisted tilt table. *Cerebrovascular Diseases.* 37(supple 2)**:**122.

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9. Declaration of Originality

Last name, first name **Saengsuwan, Jittima**

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I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.

All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such.

I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Place, date

Bern, 22.03.2016

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Signature